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# FEDERAL AND STATE RELATIONS AND THE PRACTICE OF MEDICINE*

CHRISTIAN A. HERTER†
BOSTON

ADMITTEDLY, this is a difficult subject to discuss. It is particularly difficult to compress it within the bounds of a short paper. Perhaps, however, this necessity has a certain virtue in preventing a discursive presentation that might well prove less profitable.

As one has seen the development of these relations three outstanding characteristics have appeared: the concept of public responsibility for health services for certain groups in the population; the development of a partnership in federal and state governments for financing services; and the trend to utilize the services of private physicians in providing this care.

Tradition is of no help in examining these trends. There have always been health agencies of some sort caring for various aspects of illness. The ancient Greeks pursued a community interest in health, sometimes to grim conclusions. Inadequate though early institutions in England such as Bedlam were, they nevertheless represented an attempt at a solution of a current medical problem. The treatment of scrofula by the touch of the king in old English days was nothing less than direct governmental participation in the practice of medicine.

As one approaches modern times one can see a definite change that has led to the trends mentioned above. When Jenner demonstrated successful vaccination against smallpox he established the principle of the protection of the community against mass disease. The gradual control of sewage and the purification of water supplies led to another step in the control of a hostile environment with beneficial effects on the health of man. Trudeau, in New York, at the end of the century, was more interested in treating an individual disease in an individual person, but nevertheless established a fundamental principle of communicable-disease control, the protection of the community through isolation and treatment of infected individuals. A next significant step was taken when well-baby and prenatal care, first instituted by private physicians and later supported by the state, showed the possibilities of the pure prevention of disease. In Massachusetts this work was started under the Division of Hygiene in 1917, and the first well-child conference was established in 1924.

To a great degree as an outgrowth of well-baby and prenatal clinics, the visiting nurse brought into the individual home the principle of good medical care. She was followed closely by other workers, the social worker and the nutritionist. Most recently, beginning with the work with crippled children, various services for rehabilitation have appeared. With them has come another principle of medical care: that the rehabilitation of the individual, from a condition of liability to himself to a life of usefulness, is a community responsibility.

It is evident that, whereas formerly public health was interested in people as a mass population affected by a mass disease or a noxious environment, now the interest centers on the individual. Throughout this change the essential personnel have been the private physician, the health officer and the citizen. I have chosen the word citizen very carefully; he is the individual person who makes up the communities of the land. He is more than a person because as a citizen he plays his active part in supporting the health programs of his community. The private physician has always been a bridge between the individual and the community, though by tradition he has been concerned more in his practice with the health of the individual. Of course, in his care of the individual, he is making an essential contribution to the health of the public. As a third member of the group the health officer occupies a position of responsibility to both the physician and the citizen. His duties are largely administrative, but in some fashion he must be able to see through the group back to the individuals who make up the group. The change from the mass to the individual concept means first that there must be the closest co-operation among the private physician, the health officer and the citizen and, even more, that greater reliance than ever before must be placed on the individual practicing physician.

The state stands midway between the federal Government on one side and the local community on the other. Changes in medical practice and administra-

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†Governor of the Commonwealth of Massachusetts.

tion of medical-care plans have washed over it from both sides.

On the one hand, the increasing complexity of the tools and methods of modern medical practice has led to great advance in medical care but has brought with it many problems. These are closely associated with the increasing cost of good medical care. Furthermore, the very patients requiring medical attention have changed. Every physician is aware of the increasing age of the population and of the problems that attend such a change.

On the other hand, the federal effect has come largely through the application of grants-in-aid. In the present fiscal year over $1,000,000 of federal money has been allotted to the Massachusetts Department of Public Health alone. This includes grants for general health, categorical grants and grants for the Hospital Survey and Construction (Hill—Burton) program. In general, these grants-in-aid serve roughly the following four purposes: equalizing services among states; stimulating state and local action; assuring a minimum standard throughout the country; and using state governments for administration of a particular federal program. These funds reach deeply into the services within the state and furnish care through the co-operative efforts of many hospitals and private physicians. The crippled-children service is a fine example of this. The basic policy of these services is the same throughout the states of the nation. The funds provide both for the participation of state staff personnel in local clinics and for the payment to local physicians and hospitals for actual medical care of the children. Thus, the entire gamut is run from federal financial support through state administration to practice and payment of local hospitals and private practicing physicians.

The population of Massachusetts is increasing steadily. This means that more people are actually receiving the services, either directly or indirectly, that the Commonwealth has to offer. However, this increasing population brings problems of added personnel and added administrative difficulties in general.

Largely because of the steadily increasing use of communications and travel the traditional isolation of the communities of the Commonwealth has broken down. This has led the General Court to give to the State Government certain state-wide responsibilities in the interest of uniformity. This type of legislation applies particularly to sanitary measures. Nevertheless, the basic authority in health matters still rests with the local community.

The services offered by the State are changing drastically. For example, a short space of twenty years has brought almost complete reversal of the methods of tuberculosis care. In that period the death rate from tuberculosis has been cut two thirds of its former figure, although the case rate has been cut only one third. Because of increasing home treatment of this disease, the occupancy rate of tuberculosis institutions has fallen 50 per cent.

As an additional evidence of this change the State Laboratories are looking ahead to an emphasis on viral infections that will parallel the work with the bacteria of a generation ago. None of the time-honored services remain the same today.

New ventures have engaged the State's activity, dictated by need. Some of the major ones are hospital licensing, care for the aging, care for chronic disease, the whole problem of rehabilitation, provisions for the medically needy apart from the welfare patient, the vast increase in the social services, nutrition, training, convalescent care, alcoholism, health education, safety programs, air pollution, the control of industrial waste, the problem of water resources and pollution, fluoridation and civil defense.

The State has believed, therefore, that it has four duties: to give support in every way it can to local physicians, health officers and citizens (the key work is support); to provide direct service when necessary (this, of course, is in the areas of diseases of high cost such as tuberculosis and serious mental illness); to act as the recipient of national funds and as the administrator of national programs; and to plan, evaluate and stimulate, to keep looking ahead (this in no way intends to remove the initiative from the local community but, again, to support it).

In reorienting itself to modern conditions, the State has had to deal with the expansion of old services, the introduction of new facilities, the problem of federal grants-in-aid and the matter of public responsibility.

The expansion of old services has brought administrative problems. Maintaining efficiency in the face of administrative structures too often rigid and geared to former days is at times difficult. One must find proper and efficient use also for physical facilities that have outlived their original purpose. These buildings are often too valuable to tear down and yet must in some fashion be fitted efficiently into a new plan.

The introduction of new facilities has always been accompanied by some difficulty. New staffs must be assembled and new procedures set up. Planning must be done years ahead of target date. For example, the Lemuel Shattuck Hospital began as an idea several years ago at a time when the problems of the aging population and the increasing numbers of people suffering from chronic diseases were first attracting attention. The early Osgood report indicated the need within the Commonwealth, with an estimate of 600,000 who were afflicted with a chronic disease. This was a staggering number. At the time the facilities of the State could not absorb even a portion of this number, nor were there adequate equipment and personnel for treating them. The decision was made to construct a chronic-disease hospital. As the buildings approached completion the

staff was sought. This in itself was no small job, for there are few professional workers particularly trained in this area, few who have the special interest that is demanded. Shortages were revealed in several of the ancillary professions, further complicating the staffing. However, the basic working staff was obtained, and the hospital was opened.

As everyone is aware there has been some discussion of the purpose for which the Lemuel Shattuck Hospital was built. This has been defined in the appropriation bills and in statements of policy as a hospital for the treatment of chronic disease. The goal is rehabilitation. It has not been built as a custodial institution. Its facilities and staff provide active diagnosis and therapy.

This was a new venture for the State, which, for the first time, found itself dealing with a cross-section of disease, since chronic disease is not limited to one category. Three decisions were made. The first was that admission would be only on application by the patient's own physician. The second was that the admission policy would be based on the possibility each patient held of rehabilitation. The third was that the Hospital would be associated with the teaching medical schools and schools of the ancillary professions so that the study of chronic disease could be fostered and greater hope held out for the future. This was a new approach to the solution of this problem. It was something that could not be injected with force into the over-all medical care of the Commonwealth. It had to be assimilated, to seek and to take its proper place alongside all other institutions and workers in medicine. It could not and should not be the final and only answer. It is basic to the present system of medicine that the best of care exists when there is full rapport among the State, voluntary institutions and the physicians. That association, happily, has been established and promises much.

The State has gone ahead slowly, but steadily, in opening new wards. The term rehabilitation has been interpreted to cover more than the return to full economic usefulness. The sufferer who can be helped to return to a comfortable life in his own home rather than committed to a hospital existence for the rest of his life is certainly rehabilitated. The patient who can be made free of pain for his remaining life can return to life that is vastly better than before. These, it is believed, are all degrees of rehabilitation and as such fulfill the purpose of the Hospital.

The problem of federal grants-in-aid is another one presented to the State. It might seem ungrateful to speak in such fashion of amounts of money such as I have indicated. This would be true if the federal Government itself did not realize that these programs are not without accompanying difficulties. The Hoover Commission, in its studies, has commented on both the good and the bad features of these programs.

There is no doubt that the co-operative system that is the basis for the grants has provided standards of service in many fields and in states in which such programs could not otherwise exist. There has also been definite assistance given to states poor in resources. The plan has developed a division of responsibility with the national Government giving financial aid and setting up basic standards, and the state governments sharing the fiscal support and assuming principal responsibility for administration. To a considerable degree these grants-in-aid have permitted expansion and extension of activities not possible to states unaided. In days of national emergency certain facilities stimulated and supported by federal grants within states will serve the country well if need be. Finally, the resources of advisory personnel to assist the states in their planning for these monies provide a valuable stimulus to the states' own staffs.

However, there are deficiencies. The programs too often are unrelated and unco-ordinated, partly because of individual pressure groups and partly through lack of broad planning. The relation between grants for general health and grants for specific purposes has not been determined in proper proportion to the needs of the individual states. Inevitably, because of the controls that are retained over these grants by the federal Government, the states lose large areas of discretionary powers. Policy making itself tends to become a national prerogative. Through the mechanism of matching funds — no matter how worthy or necessary that may be — state programs may be thrown out of alignment. Too much emphasis may be given to a matching program simply because of the tempting 50 per cent. A vicious circle of more tax funds to permit more grants-in-aid to require more tax funds can be established. Federal grants-in-aid can retard the development of state financial initiative but at the same time can place the state in the embarrassing position of becoming obligated to a program not entirely to its suiting. Most troublesome in recent years has been the wide variation in allotment of federal funds from year to year, and the determination of amounts assigned through rigid and complicated formulas. In spite of these deficiencies the value and necessity of the federal grant-in-aid are recognized, but one hopes for the development of less rigid formulas and greater freedom for the State administrator.

Finally, there is the matter of public responsibility that faces a state now as never before. This is an era of great knowledge shared by all people to an extent never before realized. It is a situation that possesses a tremendous emotional content. People as a whole are greatly interested in problems of health. The decisions of the health officer — in a very personal way — affect millions. Just recently, a concrete example of this has been afforded by the Salk poliomyelitis vaccine.

## Conclusions

The present era is one in which nothing remains static. Conclusions reached now regarding state, fed-

eral and individual relations may be analyzed as of this given moment. Overnight, they may change, not so much because of governmental practices and procedures but because of the new discoveries and the research being done by many eminent scientists.

Individual physicians, and their practices as reflected through health officers, can change rapidly, but governmental procedures are apt to move more slowly.

The real challenge for the future is to make governmental procedures elastic enough so that the Government can keep abreast of the physicians' findings.

# LEUKEMIA IN SURVIVORS OF ATOMIC BOMBING*

WILLIAM C. MOLONEY, M.D.†

BOSTON

THE leukemogenic effect of atomic radiation has been well established by investigations on survivors in Hiroshima and Nagasaki.[1] From 1948 to 1953, under the auspices of the Atomic Bomb Casualty Commission, observations on 75 verified cases were reported. Subsequently 17 new cases were encountered, bringing to 92 the total number of established cases occurring in survivors up to January 1, 1954 (Table 1). With these additional cases further observations on various aspects of radiation-induced leukemia are presented here.

TABLE 1. *Population of Survivors in Hiroshima and Nagasaki Cities and Prefectures, with the Distribution of 92 Verified Cases of Leukemia (1948 to 1954).*

| | EXPOSED POPULATION | DISTANCE FROM HYPOCENTER | CASES OF LEUKEMIA |
|---|---|---|---|
| | | *meters* | |
| | 2,463 | 0-999 | 23 |
| | 17,668 | 1000-1499 | 39 |
| | 36,960 | 1500-2499 | 16 |
| | 159,085 | 2500-over | 14 |
| Totals | 216,176 | | 92 |

## RESULTS OF OBSERVATIONS

### Rate of Occurrence

The increased occurrence of leukemia in survivors has been documented by earlier reports.[1,2] However, the marked difference in age distribution of survivors compared to other populations precluded a valid statistical analysis of the frequency of leukemia by the usual methods. With additional cases it became possible recently to carry out an analysis utilizing Hiroshima City data and comparing this population with itself.[3,4] There were approximately 98,000 survivors in Hiroshima City in December, 1953, and 50 cases of leukemia had been discovered in this population. These survivors were distributed according to distance from the hypocenter and were further classified in each distance zone into severely and lightly irradiated (or nonirradiated) groups. The relation between the degree of irradiation and occurrence of leukemia was strikingly demonstrated (Table 2).

### Date of Onset

In a prior report it was stated that the peak year for the occurrence of leukemia (calculated from clinical onset) was 1950, and subsequently the number of cases sharply declined.[2] Actually, on the basis of the additional cases seen in 1953, the decrease was slight in 1951 and 1952 but fell sharply in late 1953. Of the 17 additional cases studied in 1953, 1 began in 1951, 8 in 1952, and 8 in 1953. It seems safe to conclude that although leukemia will continue to appear, its rate of occurrence in survivors of atomic bombing is definitely declining (Table 3).

TABLE 2. *Occurrence of Leukemia in Hiroshima City Survivors in Relation to Distance from the Hypocenter and Severity of Radiation Complaints.**

| DISTANCE FROM HYPOCENTER | SURVIVORS | | CASES OF LEUKEMIA | | RATIO OF LEUKEMIA | |
|---|---|---|---|---|---|---|
| | SEVERELY IRRADIATED | LIGHTLY OR NOT IRRADIATED | SEVERELY IRRADIATED | LIGHTLY OR NOT IRRADIATED | AMONG SEVERELY IRRADIATED | AMONG LIGHTLY OR NOT IRRADIATED |
| *meters* | | | | | | |
| Under 2500 | 5,700 | 41,900 | 33 | 13 | 1:172 | 1: 3,223 |
| Over 2500 | 850 | 49,650 | 0 | 4 | — | 1:12,912 |

*Figures rounded to nearest 50 on basis of statistical analysis by M. Kastenbaum.[4]

### Type of Leukemia

Folley et al.[1] pointed out that the types of leukemia found in survivors presented an unusual distribution. Subsequent experience has confirmed this observation; of 92 cases 52 were acute or subacute, but of 40 chronic cases, 39 were myelogenous, and only 1 was of the chronic lymphatic variety (Table 4). Although there is no explanation for this curious distribution it should be re-emphasized that chronic lymphatic leukemia is a relatively rare disease in nonexposed Japanese.[2]

*From the Laboratories of the Atomic Bomb Casualty Commission, Hiroshima, Japan.

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†Clinical professor of medicine, Tufts University School of Medicine; associate director, first and third Medical Services (Tufts), and visiting physician, Boston City Hospital; director, Clinical Laboratories, Boston City Hospital; formerly, deputy medical director, Atomic Bomb Casualty Commission.

### Hematologic Features of Early Leukemia in Survivors

Leukemia due to atomic irradiation is similar clinically and pathologically to that in nonirradiated Japanese. As previously pointed out[5,6] the outstanding hematologic features, many months before clinical evidence of leukemia developed, were usually leukocytosis, relative lymphopenia and granulocytosis. Smears of the peripheral blood showed the presence of a small percentage of myelocytes and metamyelocytes and a striking increase in the absolute numbers of basophils.[6] In the early stages anemia was usually not present, but occasional nucleated red blood cells were seen and platelets were frequently increased. Bone-marrow studies proved to be of little diagnostic help in the early stages of chronic myelogenous leukemia.

### Biochemical Studies on Separated Leukocytes

Valentine et al.[7] found that in chronic myelogenous leukemia the glycogen content and alkaline phosphatase activity of separated leukocytes were extremely low compared to normal leukocytes. Similar findings were observed in cases of chronic myelogenous leukemia occurring in survivors. Moreover, in the early preclinical stages, the alkaline phosphatase levels were consistently as low as those found in well advanced cases of this disease.[3,6]

## Discussion

Although it is obvious that leukemia was extremely frequent in heavily irradiated survivors it should be emphasized that there were only 92 cases of verified leukemia, collected with much effort, over a period of six years among survivors of both cities. Nevertheless, the occurrence of leukemia in persons exposed to a single dose of ionizing irradiation has been of considerable biologic interest. It has been reported that cases of leukemia began to occur within a year of the atomic bombing.[8] However, no documented evidence, such as blood smears, bone-marrow preparations or autopsy material, was available to investigators of the Atomic Bomb Casualty Commission. Reports based on history alone, or on a death-certificate diagnosis, were not accepted. Therefore, although cases may have occurred among survivors in 1946 and 1947, the general disruption of medical facilities, lack of adequate records and other data made scientific studies impossible. Furthermore, hematologic surveys carried out in 1947, 1948 and 1949 in Hiroshima on approximately 1500 heavily irradiated survivors (mostly children and young adults) did not reveal any cases of leukemia at that time.[9,10] The indications are that, after the atomic irradiation, there was a "latent period" of several years. Also, in the cases of chronic myelogenous leukemia a prolonged preclinical stage, evidenced only by hematologic and biochemical changes already described, occurred. Experimentally, in mice, there is a similar "latent period" in irradiation-induced leukemia.[11] This is also true of leukemia reported sporadically in radiologists and physicists.

Table 3. *Distribution of Cases of Leukemia in Survivors, by Year of Onset.*

| Year of Onset | No. of Cases |
|---|---|
| 1947 | 5 |
| 1948 | 11 |
| 1949 | 6 |
| 1950 | 21 |
| 1951 | 20 |
| 1952 | 19 |
| 1953 | 8 |

Table 4. *Types of Leukemia in Survivors.*

| Type of Leukemia | No. of Cases |
|---|---|
| Chronic myelogenous | 39 |
| Chronic lymphatic | 1 |
| Acute myelogenous | 25 |
| Acute lymphatic | 14 |
| Acute reticulum cell | 3 |
| Acute monocytic | 4 |
| Acute type unknown | 6 |

One of the important features of leukemia in the survivors was the exact timing of the irradiation dose. (To date there has been no convincing evidence that "fall out" was a factor in the biologic effects noted in survivors of the atomic bombings.) *It should be emphasized that, whereas a large single dose of ionizing irradiation was required for leukemogenesis in the survivors, repeated smaller doses under other circumstances may well have a much greater leukemogenic effect.* In this regard there is no satisfactory explanation of how or why irradiation induces leukemia. Obviously, irradiation is only one factor, or the disease would develop in all severely irradiated survivors. The role of genetic, constitutional, nutritional, hormonal and other factors is at present a matter of speculation, but further observations on the heavily exposed survivor population may shed more light on this complex problem. Furthermore, it seems likely that other expected delayed biologic effects (such as carcinogenesis, cardiovascular renal disease and early senescence) will occur predominantly in the heavily irradiated survivors. Since less than 10 per cent of the estimated 98,000 Hiroshima City survivors were heavily irradiated, this should be a matter of some practical importance in planning of long-range future studies on survivors.

Since the inception of the program of the Atomic Bomb Casualty Commission analysis of data has repeatedly shown a discrepancy between the biologic effects and dose of irradiation as officially estimated by the physicists. It has been stated that the dose of gamma irradiation was 25 r at 2000 meters from the hypocenter and that the neutron flux only extended

to 800 meters.[13] However, biologic effects, as evidenced by carefully obtained histories, indicate that symptoms and signs of severe irradiation sickness were present in survivors out to 2500 meters. It has also been shown that lens opacities caused by irradiation have been noted at 1700 meters.[14] Since irradiation cataracts were undoubtedly caused by neutrons the neutron flux probably extended much farther and was more intense than had previously been estimated. The implications are that neutron activity may well have been involved in leukemogenesis among survivors of atomic bombing.

The cytologic and biochemical features of the early stages of chronic myelogenous leukemia in the survivors have been discussed in previous communications.[3,6] However, it is worth while to emphasize the significance of an absolute basophilocytosis in the peripheral blood and to point out that a marked increase in basophils is seldom seen except in chronic myelogenous leukemia. Moderately elevated absolute basophil counts were found in cases of polycythemia vera with leukemoid blood pictures. In these cases, however, the alkaline phosphatase activity of the separated leukocytes was greatly elevated whereas, even in the early stages of chronic myelogenous leukemia, the white-cell alkaline phosphatase values were extremely low. This early alteration of leukocyte enzyme activity may be related to the pathogenesis of the disease although this is not established. From a practical standpoint the determination of alkaline phosphatase by biochemical or histochemical methods seems to be of definite value in differential diagnosis between myelogenous leukemia and some types of leukemoid reactions.

### Summary and Conclusions

Up to January 1, 1954, 92 verified cases of leukemia had occurred among survivors of the atomic bombings in Hiroshima and Nagasaki.

The peak occurrence of leukemia in survivors was probably reached in 1951, and there was a marked decline in cases during 1953.

By analysis of data on Hiroshima City survivors, the highly leukemogenic effect of atomic radiation is demonstrated.

These data indicate that in man the leukemogenic dose of a single exposure to atomic radiation is high.

Biologic evidence in survivors points to a much more intense and extensive neutron flux than estimated physically. Neutrons as well as gamma irradiation were probably involved in the leukemogenesis.

Cytologic features in the preclinical stage of chronic myelogenous leukemia included the early appearance of a small percentage of myelocytes and metamyelocytes and a very significant basophilocytosis. Separated leukocytes showed extremely low alkaline phosphatase activity, even in the earliest stages of the disease.

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## CLINICAL AND MICROBIOLOGIC ASPECTS OF SALMONELLOSIS*

### A Study of Ninety-Five Cases in Adults and Children

George M. Eisenberg, Sc.D.,† Anthony J. Palazzolo, M.D.,‡ and Harrison F. Flippin, M.D.§

PHILADELPHIA

IT is our impression that the prevalence and clinical significance of salmonellosis, or human infections caused by salmonellas other than the typhoid bacillus, are frequently not appreciated as fully as they should be. A number of factors contribute to this situation. The first is the complexity of the methodology required to establish an unequivocal bacteriologic diagnosis and the lack of adequate facilities for the task in many laboratories, especially the smaller ones. The second is the multiplicity of clinical manifestations associated with these infections that militate against the formulation of a readily recog-

*From the departments of Laboratories and Medicine, Philadelphia General Hospital (Blockley Division), and the Section of Infectious Diseases, University of Pennsylvania School of Medicine.

†Associate in medicine, Graduate School of Medicine, University of Pennsylvania; chief, Division of Bacteriology and Immunology, Department of Laboratories, Philadelphia General Hospital (Blockley Division).

‡Assistant instructor in medicine, University of Pennsylvania School of Medicine; resident in infectious diseases, Philadelphia General Hospital (Blockley Division).

§Professor of clinical microbiology, Graduate School of Medicine, University of Pennsylvania; visiting ward physician, Department of Medicine, Philadelphia General Hospital (Blockley Division).

nizable clinical syndrome. As a result definitive diagnosis on clinical grounds alone is manifestly hazardous. Other investigators, notably Seligmann and Hertz[1] and Felsenfeld,[2] have emphasized this aspect of the problem and contributed significantly to its clarification.

The study presented below comprises a review of 95 cases of bacteriologically proved salmonella infections encountered at the Philadelphia General Hospital (Blockley Division) during the years 1947-1952. It is presented in the belief that it may serve to delineate further the clinical and laboratory aspects of diagnosis of these infections. Evidence is presented to support the suggestion that currently employed serodiagnostic procedures require modification if a greater number of salmonella infections are to be recognized.

## Description of Clinical Material

A total of 55 adults and 40 children and infants comprised the patient population of the series. The

Table 1. *Relative Frequency of Signs and Symptoms of Salmonellosis in Adults and Children.*

| Sign or Symptom | Prevalence | | |
|---|---|---|---|
| | total | adults | children |
| | % | % | % |
| **Objective:** | | | |
| Fever | 81.1 | 76.3 | 87.5 |
| Diarrhea | 63.1 | 52.7 | 77.5 |
| Vomiting | 34.7 | 27.2 | 45.0 |
| Dehydration | 10.5 | 7.3 | 15.0 |
| Splenomegaly | 4.2 | 5.5 | 2.5 |
| Roseola | 3.1 | 3.6 | 2.5 |
| Abdominal distention | 2.1 | 1.8 | 2.5 |
| **Subjective:** | | | |
| Abdominal cramps | 21.1 | 31.0 | 7.5 |
| Chills | 16.8 | 29.1 | — |
| Anorexia | 16.8 | 16.4 | 17.5 |
| Cough | 11.5 | 9.0 | 15.0 |
| Abdominal tenderness | 8.4 | 5.5 | 2.5 |
| Malaise | 8.4 | 12.7 | 2.5 |
| Nausea | 7.3 | 12.7 | — |
| Headache | 7.3 | 12.7 | — |
| Coryza | 6.3 | 7.3 | 5.0 |
| Weight loss | 4.2 | 3.6 | 5.0 |
| Muscle pain | 1.1 | 1.8 | — |

fact that slightly more than 42 per cent of the patients were in the pediatric age group corroborates the experience of others[3-6] regarding the high degree of susceptibility of infants and children to salmonellosis.

In the adult group the patients ranged in age from twelve to eighty-five years, with an average age of forty-four and seven-tenths years. The group consisted of 64 per cent males and 40 per cent Negroes. The average duration of illness before hospitalization was eight days, with a range of two to forty-two days.

In the pediatric group the average age was one and four-tenths years, the youngest patient being nine days old and the oldest seven years. There were 50 per cent males and 77.5 per cent Negroes. Five days was the average duration of illness before hospitalization, with a range of one to twenty-eight days.

Neither group differed significantly in sex or race. Analysis of factors concerning seasonal distribution of cases seemed unwarranted in view of the comparatively small size of the series.

Table 2. *Mortality in Salmonellosis.*

| Case No. | Age of Patient | Salmonella Serotype | Cause of Death |
|---|---|---|---|
| | yr. | | |
| 1 | 71 | *S. choleraesuis* | Septicemia |
| 2 | 41 | *S. choleraesuis* | Congestive heart failure & bacterial endocarditis |
| 3 | 37 | *S. typhimurium* | Septicemia |
| 4 | 41 | *S. daytona* | Congestive heart failure, with typhoidlike picture; no specific therapy. |
| 5 | 85 | *S. enteritidis* | Acute purulent pericarditis |
| 6 | 68 | *S. montevideo* | Shock, dehydration & aspiration of vomitus |
| 7 | ½ | *S. newport* | Profound toxemia, with severe dehydration |
| 8 | 2½ | *S. münchen* | Perforation of colon, with peritonitis |

## Signs and Symptoms

In view of the multiplicity and diversity of signs and symptoms manifested in cases of salmonellosis, it was believed that their occurrence in this series would be of particular interest. Their prevalence in the group as a whole and in the adult and pediatric groups separately, as well as their characterization for subjectivity or objectivity, is shown in Table 1. It is seen that fever and diarrhea were most often encountered in both the adult and pediatric groups, diarrhea being significantly more common in the latter than in the former. Furthermore, the signs of roseola and splenomegaly, commonly associated with typhoid fever, occurred relatively infrequently in this series. With the exception of anorexia and cough subjective signs and symptoms were less commonly seen in the pediatric cases than in the adults, as was expected.

## Associated Diseases and Complications

It is not an uncommon experience of investigators working in a municipal institution, where a high percentage of the patient population comes from lower socioeconomic levels, to find more than one pathologic entity in a large proportion of the patients. This was our experience with 52 per cent of all patients in this series — 74 per cent of the adult group and 27 per cent of the pediatric group. The nature of the associated diseases was quite varied and in many cases

was actually the condition that prompted the patient to seek hospitalization. Since it is thought that tabulation of the specific types of associated diseases would not contribute in great measure to the primary objectives of this study, such an enumeration is omitted.

In this series there were only two complications that were considered to be directly attributable to the salmonellosis. One was a case of *Salmonella münchen* infection in a child with perforation of the colon and subsequent fatal peritonitis. The second was an adult patient from whom *S. typhimurium* was isolated and whose gastroenteric symptom complex was followed by central-nervous-system signs and symptoms of an encephalitic nature.

*hattan* (a child). No cases of *S. choleraesuis* carriers were encountered, a circumstance that is general experience.[8,9]

## Therapy

Unfortunately, the results of therapy in this series do not lend themselves readily to analysis. This situation is due to the number and diversity of antibacterial drugs used, either singly or in combination, a circumstance that may be attributed to several factors. Precise diagnosis was delayed in many cases. Moreover, the period covered by this study (1947-1952) witnessed the introduction of the broad-spectrum antibiotics, chloramphenicol, chlortetracycline and oxytetracycline, which were employed with ever-

Table 3. *Frequency and Distribution of Clinical Syndromes and Associated Salmonella Group in Salmonellosis.*

| Salmonella Serogroup | Syndrome of Gastroenterocolitis | | Syndrome of Bacteremia or Septicemia with Bone Localization | | Syndrome of Bacteremia or Septicemia with Renal Localization | | Syndrome of Bacteremia or Septicemia with Pericardial Localization | | Syndrome of Bacteremia or Septicemia with Abscess | | Syndrome of Bacteremia or Septicemia without Localization | | Typhoidlike Syndrome | | Carriers | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Adults | Children | Adults | Children | Adults | Children | Adults | Children | Adults | Children | Adults | Children | Adults | Children | Adults | Children |
| B | 9 | 20 | | | 1 | | | | 1 | | | | | | 1 | |
| $C_1$ & $C_2$ | 18 | 9 | 2 | 1 | 2 | | | | 2 | | 7 | 4 | 3 | | 1 | |
| D | 2 | 1 | | | | | 1 | | | | | | | | | 1 |
| $E_1$ & $E_2$ | 2 | 2 | | | | | | | 2 | | | 1 | | | | |
| Multiple salmonellas involved | — | 1* | — | — | — | — | — | — | — | — | — | — | — | — | 1† | — |
| Totals | 31 | 33 | 2 | 1 | 3 | — | 1 | — | 5 | — | 7 | 5 | 3 | — | 3 | 1 |
| All cases | 64 | | 12 | | | | | | 12 | | | | 3 | | 4 | |

*Became *S. manhattan* carrier.
†*S. tennessee* carrier.

## Mortality

When the fatal cases in the series were analyzed two conclusions became apparent: that the deaths occurred among the very young and older, debilitated patients and that the largest number were associated with salmonellas of serogroup C. These conclusions confirm observations by others.[4,6-9]

Among patients of this series there was a total mortality of 11.6 per cent, but if cases in which the fatal outcome was neither partially nor directly attributable to the salmonellosis are excluded, the mortality is reduced to 8.4 per cent (6 adults and 2 children). A brief summary of the relevant data is given in Table 2.

## Carriers

Five patients (5.3 per cent) in the series were classified as salmonella carriers. Three of these, 2 adults with *S. montevideo* and *S. derby* respectively and 1 child with *S. enteritidis*, were asymptomatic carriers. The remaining 2 were admitted to the hospital with symptoms, were found to have mixed salmonella infections, responded clinically to therapy, but subsequently had stool cultures that were repeatedly positive for *S. tennessee* (an adult) and *S. man-*

increasing frequency in cases in which infection by a gram-negative organism was suspected. However, a few observations can be made. Sixteen patients recovered when treated only with supportive measures and without benefit of specific antibacterial agents. Fifty-one received more than one specific antibacterial agent, among which were included sulfonamides, penicillin, streptomycin, chloramphenicol, chlortetracycline and oxytetracycline.

## Discussion

### Clinical Diagnosis

Much emphasis has been placed upon the protean manifestations of salmonellosis, so that the clinician must be aware of the possible existence of this infection if the presumed diagnosis is to be verified by appropriate bacteriologic and serologic studies. Recognizing the need for criteria that could help in clinical diagnosis, Seligmann, Saphra and Wassermann,[8,9] Bornstein[10] and Felsenfeld[2] suggested that the signs and symptoms encountered in salmonellosis be classified into several clinical syndromes. With slight modification, these are as follows:

Gastroenterocolitis, which can cause symptoms ranging from mild diarrhea to a choleralike picture.

Bacteremia or septicemia, either with or without extraintestinal localization in meningeal, renal, pulmonary, pleural and similar sites.

A clinical picture similar to but usually milder than that seen in the typical case of typhoid fever.[10]

Carriers, either convalescent or asymptomatic.

The frequency and distribution of clinical symptoms, adjudged on the basis of the foregoing classification, together with the associated salmonella serogroup, are shown in Table 3. It is evident that the gastroenterocolitis syndrome predominated in both the adult and pediatric groups since it was seen in 67.4 per cent of the patients. Other investigators have reported a similar experience.[5,8,9] Owing to the frequency of fever and diarrhea as presenting signs it is pointed out that, though not always associated, the occurrence of diarrhea accompanied by fever should prompt the clinician to include salmonellosis in his differential diagnosis and to request appropriate laboratory studies either to support or to rule it out.

The reported invasiveness of *S. choleraesuis*[1,2,9,11] was substantiated in this study. Salmonella organisms of Group C were involved in 18 of 24 cases manifesting bacteremia with or without extraintestinal localization, the most frequently occurring serotype being identified as *S. choleraesuis*.

A point of interest revolves around the 3 cases in which the typhoidlike syndrome was observed and in which the etiologic agent was identified as belonging to Group C. In contrast, others have reported that paratyphoid bacilli A and B are the most common serotypes associated with this clinical picture.[8] It is doubtful if this divergence is really conflicting, since no infections due to paratyphoid A and only one due to paratyphoid B were encountered in our series. In addition it serves to emphasize the hazard associated with the attempt to identify a particular serotype with a specific clinical picture. Certainly, there should no longer be any doubt that there is no sharp demarcation and that overlapping is the rule rather than the exception. The essence of the matter is the fact that salmonellas are capable of producing any of the syndromes listed and that age and individual resistance of the patient are more important in determining the clinical picture and ultimate outcome of the disease.

### Laboratory Diagnosis

Certainly, there can be no argument that the best evidence of infection with salmonellas is the isolation and identification of the specific incitant. However, the probability of successful laboratory cultivation is frequently determined not only by the available facilities but also by the stage of the disease during which body-fluid specimens are taken for bacteriologic examination. Bacteriologic diagnosis is often made more difficult or even impossible by the unjustifiedly premature institution of antimicrobial therapy before collection of specimens for examination. As a result, it is not surprising to encounter cases with clinical evidence of salmonellosis in which isolation of a causative organism cannot be accomplished. In such cases the examination of blood serum for agglutinating antibodies often provides indirect evidence of infection, particularly when multiple studies demonstrate a significant rise or fall in titer of such antibodies. Antibody demonstration also serves as further corroborative evidence of salmonellosis in cases that yield positive cultures.

TABLE 4. *Antigenic Composition and Prevalence of Salmonellas.*

| Serogroup | Type | No. of Cases* | O Antigen | H Antigen | |
|---|---|---|---|---|---|
| | | | | Phase I | Phase II |
| B | *S. typhimurium* | 24 | (I)†, IV, (V)†, XII | i | 1, 2, 3 |
| | *S. derby* | 7 | (I)†, IV, XII | f, g | — |
| | *S. schoitmülleri* | 1 | (I)†, IV, (V)†, XII | b | (1, 2)† |
| $C_1$ | *S. choleraesuis* | 23 | VI, VII | (c)† | 1, 5 |
| | *S. tennessee* | 5 | VI, VII | z29 | — |
| | *S. oranienburg* | 4 | VI, VII | m, t | — |
| | *S. montevideo* | 4 | VI, VII | g, m, s | — |
| | *S. bareilly* | 1 | VI, VII | y | 1, 5 |
| | *S. daytona* | 1 | VI, VII | z | 1, 5 |
| $C_2$ | *S. newport* | 8 | VI, VIII | (e, h)† | 1, 2, 3 |
| | *S. münchen* | 1 | VI, VIII | d | 1, 5 |
| | *S. manhattan* | 1 | VI, VIII | d | 1, 5 |
| | *S. litchfield* | 1 | VI, VIII | l, v | 1, 2, 3 |
| D | *S. enteritidis* | 4 | (I)†, IX, XII | g, m | — |
| | *S. panama* | 1 | I, IX, XII | l, v | 1, 5 |
| $E_1$ | *S. give* | 3 | III, X, XXVI | l, v | 1, 6 |
| | *S. anatis* | 3 | III, X, XXVI | e, h | 1, 6 |
| $E_2$ | *S. newington* | 1 | III, XV | e, h | 1, 6 |

*Does not include 2 cases in which multiple salmonellas present.
†Signifies that indicated antigen may be absent.

The vast majority of salmonellas isolated from infections in this country belong to Group B, C or D or to Group E.[12] This distribution was also observed in the present series (Table 4). It would be logical to suppose that laboratory agglutination procedures would therefore employ a battery of antigens selected to reveal antibodies to the major somatic antigens that characterize each of these serogroups. To our knowledge there are no commercially available febrile antigens that can be used in the laboratory to accomplish this, so that if agglutination studies are done with such antigens only, certain types of salmonella infection escape serologic detection. The reason for this statement becomes obvious after consideration of the following paragraphs.

The Kauffmann–White schema[13] reveals that somatic antigen XII occurs in all salmonellas comprising Groups A, B and D. With very few exceptions antigen VI is characteristic of Group C whereas all members of Group E possess somatic antigen III. It is logical to expect that, after infection, antibodies specific for these antigens should appear. Thus, a serum reactive in significant titer toward an antigen known to contain component XII could be presumed to have been produced as a result of infection by an unknown organism also possessing XII in its antigenic composition.

In the past, routine agglutination studies in our laboratories on serums of patients suspected of having enteric fever included the use of the following diagnostic antigens*:

Typhoid O antigen (containing antigenic components IX and XII).

Typhoid H antigen (containing flagellar d antigen).

Paratyphoid A antigen (containing flagellar a antigen).

Paratyphoid B antigen (containing flagellar b, 1, 2 antigen).

Significant agglutination of the typhoid O antigen by an unknown serum could be interpreted as indicating antibodies to Group A, B or D. Agglutination of the typhoid H antigen could be interpreted as indicating antibodies to flagellar d antigen, which occurs only in a few salmonellas (three strains in Group B, three strains in Group C, one strain — *S. typhosa* — in Group D and two strains in Group E). Hence, with the exception of *S. typhosa*, the use of typhoid H antigen alone has little serodiagnostic value with most salmonellas. Agglutination of flagellar a could be interpreted as indicative of antibodies to flagellar a, an antigen that also occurs in few salmonellas (*S. paratyphi* A, rare in the United States, three strains in Group B, two strains in Group C and four strains in Group D). Finally, agglutination of flagellar b, 1, 2 could be interpreted as indicating antibodies to flagellar b antigen, either the specific or the nonspecific phase. Flagellar b antigens occur in four strains of Group B (notably *S. schottmülleri*), two strains of Group C and one strain each in Groups D and E. Aside from its significance for *S. schottmülleri* infections, flagellar b antigens would not be helpful in demonstrating antibodies to a very large number of salmonellas.

Nevertheless, the incorporation of all four diagnostic antigens listed above into the serodiagnostic battery will reveal the presence or absence of antibodies to most Group A, B and D salmonellas occurring in infections in this country. However, they will fail to demonstrate antibodies specific for most members of Groups C and E. This conclusion is supported by our experience in this series. Forty-nine cases of salmonellosis were found to be due to salmonella organisms of Group C. In 16 of these patients no serum agglutinations were performed. Among the remaining 33, there were 10 whose serum agglutinin content was evaluated solely with the routine antigens. None of these gave evidence of antibodies for salmonella. In the remaining 23 cases agglutination studies included an antigen for Group C in addition to the routine antigens. Twenty patients (87 per cent) showed significant antibody titers for the C antigen and insignificant titers for the routine antigens. Similar observations have been made in cases of salmonellosis in which Group E incitants were involved. As a consequence, we have broadened the scope of the battery of antigens in use in our laboratory for serodiagnosis of suspected salmonellosis to include appropriate antigens for infections due to Groups C and E. We consider ourselves justified in urging others to follow the same course, in view of the recognized pathogenicity and high invasiveness of Group C salmonella, especially *S. choleraesuis*.[14]

In conclusion it may be appropriate to point out that the problem of salmonellosis is of interest not only to the microbiologist, clinician and public-health physician but also to the surgeon, since it may present itself in the guise of various pseudosurgical syndromes. Although specific cases of this situation were not encountered in this series others[1,5] have reported cases of salmonellosis misdiagnosed as appendicitis, cholecystitis, salpingitis and so forth. In view of the complex problems involved in both the laboratory and the clinical diagnosis of salmonellosis, and since an unequivocal solution of the problem is not immediately apparent, the clinician and the surgeon should be constantly aware of the possibility and should obtain proper laboratory studies.

*Available from Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

## Summary

Ninety-five bacteriologically proved cases of salmonellosis in adults and children, as seen at the Philadelphia General Hospital (Blockley Division) between 1947 and 1952, are analyzed for their clinical and microbiologic features. The clinical data are evaluated in the light of experience of others, with special emphasis on the problem of diagnosis. Evidence is presented to support the suggestion that currently employed serodiagnostic procedures should be modified to ensure recognition of infections caused by a greater number of serogroups.

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# URETEROCELE AS A CAUSE OF ABDOMINAL PAIN*

STUART L. SCHEINER, M.D.,† JOSEPH ROGERS, M.D.,‡ AND B. G. CLARKE, M.D.§

BOSTON

URETEROCELE, though not a common disorder, may be a perplexing diagnostic problem in adults. The present report concerns 5 cases in which the patients were treated unsuccessfully on the basis of mistaken or incomplete diagnosis of other conditions until urologic investigation disclosed ureterocele as the underlying disorder. In Case 1 the symptoms simulated those of inguinal hernia and the complications of its repair. In Case 2 pain caused by ureterocele was thought to be due to prostatovesiculitis. The symptoms of pyelonephritis in Case 3 could not be controlled until the obstructive lesion was diagnosed at cystoscopy. Another patient (Case 4) was believed to have gall-bladder disease until intravenous pyelography disclosed obstruction of the right kidney and ureter by a ureterocele. In Case 5 unilateral ureterocele resulted in development of a contracted pyelonephritic kidney, which was regarded as the cause of hypertension of Goldblatt type.

## CASE REPORTS

CASE 1 (89-825). A 51-year-old man had complained of pain in the left testis and left groin varying in intensity but constant in character for 8 years. A few months after the pain first appeared he had sought medical advice and had been told that he had an inguinal hernia. Operation, presumably for hernia, did not relieve the pain, and 1 year later he was told that the inguinal ring had been reconstructed too tightly at operation. A 2d operation in the inguinal region resulted in a hematoma of the scrotum and of the abdominal wall that required surgical drainage.

Atrophy of the testis ensued, but the pain remained. X-ray studies of the upper and lower bowel 6 months after the operation and again 7 years later failed to disclose its cause. The patient sought the advice of a urologist, who treated him for chronic prostatovesiculitis without avail.

At the time of admission to the hospital urinalysis and examination of the prostatic secretion yielded no evidence of infection. An intravenous pyelogram (Fig. 1) showed bulbous dilatation of the terminal left ureter. The diagnosis of ureterocele was verified at cystoscopy. Prompt and sustained relief of pain followed transurethral ureteral meatotomy with the use of the cystoscopic scissors.

CASE 2 (78-215). For 2 years this 32-year-old man had had pain in the lower back and right lower part of the abdomen of almost constant character. At the age of 12 he had been treated for a urinary infection. Urinary and prostatic secretions were uninfected at the time of the present admission to the hospital. Physical and other laboratory examinations were negative. X-ray study of the upper and lower bowel, gall bladder, spine and pelvis did not reveal the cause of the pain. Sigmoidoscopic study of the lower bowel disclosed normal structures.

An intravenous pyelogram revealed normal kidneys and upper ureters but showed bulbous dilatation of the terminal ureter on each side (Fig. 2). At cystoscopy a ureterocele was found on each side, and bilateral ureteral meatotomy was done by means of the incisor electrode. A median bar, presumed to be an associated congenital anomaly, was found at the posterior neck of the bladder and resected. After operation the patient was free of pain and voided with a more forceful urinary stream. Study 7 weeks later showed uninfected urine and normal intravenous pyeloureterograms. Endoscopic inspection of the bladder disclosed patent, normally functioning ureteral orifices.

FIGURE 1. *Bulbous Dilatation of the End of the Left Ureter. The ureterocele caused symptoms successively thought to be due to inguinal hernia and prostatovesiculitis.*

CASE 3 (60-936). This 47-year-old woman complained of pain in the left flank, lower abdomen and groin of six weeks' duration. At first it had been constant and dull and then severe and colicky and accompanied by fever. A physician, who had originally suspected a ureteral calculus, discovered pus in the urine and began treatment with a sulfonamide compound. The blood pressure was 220/110. The patient had not been aware of the hypertension before admission, and it persisted after treatment of the urinary infection and the ureterocele. The urine contained numerous leukocytes in the sediment, and *Escherichia coli* was demonstrated in cultures. Intravenous pyelograms disclosed no abnormality.

In a search for the cause of the urinary infection cystoscopy was done, and a typical ureterocele found on the left. Retrograde injection of dye through the pin-point orifice demonstrated a characteristic deformity at the lower end of the left ureter (Fig. 3). Transurethral ureteral meatotomy was done with the cystoscopic scissors. Thereafter, the patient remained free of symptoms. The urine became sterile, and at cystoscopy 10 weeks later a slightly patulous but normally functioning ureteral orifice was found.

*From the departments of Urology and Medicine, New England Center Hospital and Tufts University School of Medicine.

†Intern in surgery, New England Center Hospital.

‡Assistant professor of medicine, Tufts University School of Medicine; physician, New England Center Hospital.

§Assistant professor of urology, Tufts University School of Medicine; urologist, New England Center Hospital.

CASE 4 (59-092). A 26-year-old housewife had been studied by her physician on account of repeated attacks of gnawing pain in the right upper quadrant of the abdomen that had recurred periodically for 5 years and were generally of 6 to 10 hours' duration and not clearly related to meals or any particular activity or posture. The pain

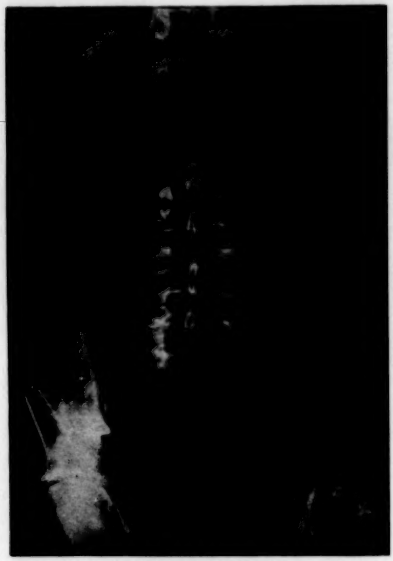

FIGURE 2. *Bilateral Ureterocele Causing Pain Thought to Be of Prostatic Origin.*

radiated to the upper back on the right and was often accompanied by nausea and gaseous eructations. There was no history of jaundice or of abnormality of stools.

The physical examination was in no way remarkable, and the blood pressure was normal. Blood counts, urinalyses and blood sedimentation rate were normal, and the serum reaction for syphilis was negative.

The physician suspected disease of the gall bladder, but a cholecystogram was normal. Further x-ray study gave no evidence of disease in the esophagus, stomach, small bowel or colon. An intravenous pyelogram showed hydronephrosis and hydroureter on the right. A large ureterocele could be seen as a negative shadow outlined within the dye-filled bladder. Transurethral resection of the lesion was followed by considerable improvement. X-ray examination 6 months later showed persistent although considerably lessened hydronephrosis on the right.

CASE 5 (64-521). This 34-year-old woman was first known to have hypertension 8 years before admission to the hospital. There had been no symptoms in the past to suggest urinary infection. The blood pressure was 220/110. A sedation test showed considerable lability of the hypertension. The benzodioxane test gave no evidence of pheochromocytoma. There were no clinical or laboratory signs of cardiac involvement. Early retinal changes were noted. The urine was uninfected at the time of hospitalization, and no albumin or significant formed elements were found in the sediment. The phenolsulfonphthalein excretion and blood urea nitrogen were normal. Intravenous and retrograde pyelography disclosed a normal kidney and ureter on the right but showed that the left kidney was small and irregularly contracted, with some clubbing of the calyxes and narrowing of the infundibula. Renal function on the left, estimated by rate of excretion of contrast medium (Urokon), was appreciably lessened. At cystoscopy a ureterocele on the left, somewhat distorted by scar, was found. A ureterogram suggested bulbous dilatation of the end of the left ureter. Because of the likelihood that unilateral pyelonephritis had caused the hypertension, nephrectomy was advised but was refused by the patient.

## DISCUSSION

The chief symptom of ureterocele in adults is pain in the abdomen, groin or flank. Other symptoms depend upon the presence or absence of complications and are not specific. Such complications may include pyelonephritis, cystitis, hydronephrosis, stone forma-

FIGURE 3. *Ureterocele on the Left Associated with Intractable Pyelonephritis.*

tion within the ureterocele sac and prolapse of the sac to obstruct the urethra in ball-valve manner. In female patients the ureterocele may prolapse through the urethral meatus to present itself as a mass in the vulva.[1] In view of the variety of symptoms that ureterocele may cause its presence may be suspected during the investigation of a considerable variety of complaints.

Ureteroceles are probably nearly all of congenital origin. Congenital etiology is supported by the high degree of bilaterality (15 per cent on the average and 16 per cent in Campbell's[2] 80 cases), by its common appearance in early life and by its frequent

association with other anomalies, of which duplication of the ureter is the commonest. Riba[3] has reported cases of bilateral ureterocele in identical twins, lending further support to the congenital theory of origin. When associated with ureteral duplication, the ureterocele originates from the upper ureter. Among the 37 cases of Thompson and Greene[4] only 1 was recognized as definitely having been acquired.

Ureterocele, as a pathologic entity, has two essential elements: a pin-point narrowing of the ureteral orifice and relaxation, prolapse and dilatation of the wall of the distal ureter. The lesion appears to occur with equal frequency on either side of the body, and somewhat more commonly among females than males.[5,6] It is occasionally asymptomatic, and its existence suspected only as the result of pyelograms or cystoscopic examinations made during the study of other conditions.

Intravenous pyelograms may delineate the lesion in some cases, but final diagnosis rests upon cystoscopy. When the ureter is at rest the pin-point orifice may be seen, often surmounting a small zone of heaped-up bladder wall. When filled by peristalsis the ureterocele balloons into the cavity of the bladder, and urine is ejected in a fine stream through the pin-point opening. The cystoscopist may miss the lesion if he does not observe the full cycle of ureteral peristalsis during his examination. In excretory pyelograms the ureterocele may be outlined positively as a "cobra-head" or "spring-onion-tip" deformity of the dilated distal ureter, or negatively as the protruding ureteral mass produces a filling defect in the bladder. The size of the lesion, as described in Gutierrez's[7] classic paper, may range from that of a hazel nut to that of a large orange.

Treatment, in adults, usually may be accomplished transurethrally by ureteral meatotomy with scissors or incisor electrode, by loop resection or by fulguration to form a patent and normally functioning orifice. In infants and children, a similar maneuver may be accomplished by a transvesical approach although cystoscopic operations have also been used with success. As Gross and Clatworthy[8] point out, slitlike enlargement of the orifice at open operation is less likely than excision of the ureterocele to lead to an incompetent ureterovesical-valve mechanism. Special circumstances, and particularly complications, may necessitate variations in surgical attack.

### Conclusions

Ureterocele in adults is manifested chiefly by abdominal pain, which may simulate a variety of other conditions. Intravenous pyelography is often helpful in establishing the diagnosis but final recognition of the lesion depends on cystoscopy.

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# MEDICAL PROGRESS

## HEMORRHAGIC STATES DURING PREGNANCY (Concluded)*


Oscar D. Ratnoff, M.D.,† Jack A. Pritchard, M.D.,‡ and Joan E. Colopy, B.S.§

Cleveland, Ohio


### Amniotic-Fluid Embolism

A second cause of generalized bleeding during parturition is amniotic-fluid embolism. In this condition, first described in 1941 by Steiner and Lushbaugh, amniotic fluid enters the maternal circulation just before, during or after childbirth. In about two thirds of the reported cases, the women have been thirty years of age or older, and most have been multiparous. Moreover, in at least half the cases, labor has been excessively severe and rapid. Typically, in one group of cases severe respiratory distress, with dyspnea and cyanosis, suddenly develops and the patient dies within a matter of minutes. In other cases the patient gradually slips into shock during the first few hours post partum, there is gross uterine hemorrhage, and, despite supportive measures, the patient usually dies. At autopsy, evidence of embolization of the maternal circulation by amniotic fluid is present; lanugo hairs and desquamated fetal epithelium, the so-called "squames," can be found in the mother's pulmonary vessels.

Weiner and Reid[37] reviewed 22 fatal cases of amniotic-fluid embolism. In 7, death occurred almost instantly. Among the 15 patients who survived the


*From the departments of Medicine and Obstetrics and Gynecology, Western Reserve University School of Medicine and University Hospitals.



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†Assistant professor of medicine, Western Reserve University School of Medicine.

‡Assistant professor of obstetrics and gynecology, Western Reserve University School of Medicine.

§Research assistant, Western Reserve University School of Medicine.

period of delivery itself 13 had severe hemorrhagic manifestations. Severe uterine hemorrhage was the rule, but in some cases, evidence of a generalized bleeding tendency was present. Weiner and Reid studied the properties of amniotic fluid, and observed that it was highly thromboplastic in vitro, a finding confirmed by Rendelstein, Frischauf and Deutsch.[38] For this reason Weiner and Reid suggested that the bleeding tendency in amniotic-fluid embolism might be due to intravascular defibrination. Experimentally, Rendelstein and his associates were able to defibrinate dogs by the intravenous injection of amniotic fluid,[38] supporting this point of view.

Hypofibrinogenemia has now been demonstrated in several patients with amniotic-fluid embolism.[24,39-42] The findings in 8 cases have been reviewed by Jackson, Hartmann and Busby.[24] In addition to varying degrees of hypofibrinogenemia 2 patients had thrombocytopenia, and 1 had hypoprothrombinemia in combination with a delay in the clotting time of mixtures of plasma and thrombin. These data are compatible with the view that the coagulative defect in such patients is due to the thromboplastic action of the infused amniotic fluid on the maternal blood. Excessive plasma fibrinolytic activity has been reported in 2 patients with amniotic-fluid embolism,[40,41] and we have observed this phenomenon in 2 other cases. However, excessive fibrinolysis is not invariably present in association with the hypofibrinogenemia of amniotic-fluid embolism, and amniotic fluid itself is not fibrinolytic.[38,43] As in the patients with premature separation of the placenta it seems reasonable to relate the excessive plasma fibrinolytic activity in patients with amniotic-fluid embolism to the concomitant shock, combined with the post-partum state.

These patients should be treated for shock in the usual manner. In addition they should be given an intravenous injection of 4 to 6 gm. of fibrinogen or, if this is not available, blood or plasma transfusions. The injections of fibrinogen may be repeated as often as is necessary to maintain an adequate concentration of fibrinogen in the plasma; a concentration of 150 mg. per 100 cc. or more should be satisfactory. However, restoration of the normal concentration of fibrinogen is not of itself necessarily an adequate measure against the hemorrhagic tendency. Two patients treated in this manner died fifteen and fifty-two hours post partum respectively. The latter of these patients had, in addition to hypofibrinogenemia, an unexplained prolongation of the clotting time and severe thrombocytopenia. It is possible that the thrombocytopenia was the result of massive transfusion with 19 liters of citrated bank blood.

Supracervical or total hysterectomy was performed in 3 cases studied because of the possibility that hemorrhage was coming from an unsuspected uterine tear. In each case it was impossible to control bleeding from the operative site, and the patients died.

Amniotic-fluid embolism, however, is not necessarily fatal. A number of cases of what appeared to be this condition have been described in which patients, treated by nonoperative means, survived.[41,42] Two such patients were recently observed at University Hospitals of Cleveland.

A 36-year-old woman was admitted in the 8th month of her 3d pregnancy because the fetal membranes had ruptured spontaneously. A large clot formed in blood drawn at this time. On the following day tumultuous labor ensued spontaneously, and a living infant was delivered within 25 minutes, followed 2 minutes later by a normal placenta. Subsequently, there was excessive uterine bleeding. The blood pressure, 30 minutes after delivery, was 90/40, and the pulse rate 140 per minute. The blood pressure fell within the following hour to a low of 70/40, with a persistent tachycardia; the patient was semicomatose and had air hunger. Blood drawn 40 minutes after delivery did not clot. Transfusion of blood was started. Two hours after delivery venous blood formed a very small clot, and the concentration of fibrinogen was 40 mg. per 100 cc. of plasma. No abnormal fibrinolysis was demonstrable at this time. Twenty minutes later 3 gm. of fibrinogen was injected intravenously while blood transfusion was continued; vaginal bleeding significantly lessened. Three hours and 20 minutes post partum, the concentration of fibrinogen in the plasma was 67 mg. per 100 cc. and, 6 hours later, when the patient was clearly out of shock, 124 mg. per 100 cc. Therapy included the transfusion of 2 liters of citrated blood, injections of Wyamine and intravenous infusion of saline and glucose solutions as well as human fibrinogen. The subsequent course was uneventful.

It is of interest that in some patients who appear to have had amniotic-fluid embolism, hemorrhagic symptoms appear when the concentration of fibrinogen in the plasma does not seem to be sufficiently low to account adequately for the ineffective hemostasis. For example, Chessin and Greenwald[44] treated a patient with pre-eclampsia in whom excessive vaginal bleeding was noted several minutes after delivery. The episiotomy wound oozed, and her whole blood did not clot, but the concentration of fibrinogen was 150 mg. per 100 cc.; a fibrinolysin was thought to be present. We have observed a strikingly similar case. However, since these patients recovered, the diagnosis of amniotic-fluid embolism was only inferential, and the pathogenesis of the observed changes may in fact have been quite different.

The experience with these nonfatal cases compared to those in which hysterectomy was performed to control uterine bleeding suggests that nonoperative therapy is to be preferred.

#### Intrauterine Retention of a Dead Fetus

A third cause of a hemorrhagic state during pregnancy is intrauterine death of the fetus. Only a handful of patients with this condition have been studied, but it is already clear that this syndrome may have a number of variations. In 1950 Weiner, Reid and Roby[45] described 3 patients in whom intrauterine fetal death occurred in the sixth month of pregnancy. Eight to eleven weeks later spontaneous delivery took place. In each case severe uterine hemorrhage resulted, accompanied by hypofibrinogenemia and, in 2 cases, evidence of a generalized bleeding tendency. DeLee, in 1901, described a similar case in which the significance of the clinical observations was not appreciated.

Since the report of Weiner and his associates other cases of hemorrhagic disease associated with intrauterine fetal death have been recorded. The rate of hypofibrinogenemia in association with the retention of a dead fetus is relatively high. The 3 cases referred to above[45] were among 15 patients in whom fetal death had occurred. In our own experience hypofibrinogenemia has been detected in 8 of 31 patients with a retained dead fetus, but 3 of these patients were studied initially because of a hemorrhagic tendency.[45a] Hypofibrinogenemia has not been reported in cases in which fetal death occurred earlier than the fourth month of gestation, nor has hypofibrinogenemia been noted in less than five weeks after the apparent death of the fetus. In the first cases described, fetal death was associated with maternal Rh isoimmunization.[48] Subsequently, however, cases have been observed in which isoimmunization did not appear to be a factor.[24,45a,46]

In 1 case[47] hypofibrinogenemia was present for at least four and a half weeks, until supracervical hysterectomy was performed. This case was remarkable for the constancy of the hypofibrinogenemia, confirmed by electrophoretic study (Fig. 3). In 3 other recent cases at University Hospitals serial studies after the

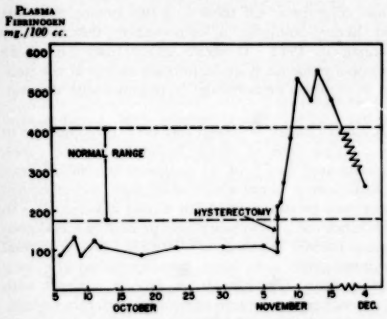


FIGURE 3. *Concentration of Fibrinogen in the Plasma of a Patient in Whom Fetal Death Occurred at about Twenty-Eight Weeks' Gestation.*

*Approximately 5 gm. of fibrinogen was given just before and during hysterectomy.*[5]

death of the fetus revealed a gradual decrease in the concentration of fibrinogen in the maternal blood until hysterotomy was performed (Fig. 4) or spontaneous delivery occurred. These 4 cases suggest that hypofibrinogenemia may actually have been present for some time in some of the patients in whom the diagnosis was first made at the time of labor, instead of developing acutely, as is assumed to occur in premature separation of the placenta and amniotic-fluid embolism.

The mechanisms responsible for the hypofibrinogenemia are not known. One hypothesis suggested is that the maternal fibrinogen is destroyed as the result of proteolysis. In a few of the reported cases abnormal plasma fibrinolytic activity was detected. In 1 patient whom we studied just after delivery, the concentration of fibrinogen in the plasma was 102 mg. per 100 cc.; a clot formed by the recalcification of the patient's plasma dissolved within seven hours. Furthermore, Vecchietti[48] observed that the amniotic

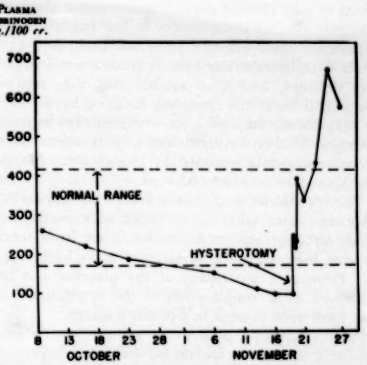


FIGURE 4. *Concentration of Fibrinogen in the Plasma of a Patient in Whom Fetal Death Occurred at about Twenty-Five Weeks' Gestation.*

*An injection of 3.5 gm. of fibrinogen was given just before and during hysterotomy.*[45a]

fluid of a patient whose fetus had been dead for some weeks was fibrinolytic. However, normal amniotic fluid and that of 2 patients with a retained dead fetus were not fibrinolytic.[23,45a] We have not been able to detect significantly abnormal fibrinolytic activity in the blood of 5 patients with hypofibrinogenemia associated with a retained dead fetus. The failure to demonstrate any abnormal fibrinolytic activity in cases studied over a period of many weeks suggests that fibrinolysis is not the mechanism responsible for the hypofibrinogenemia. It is possible, however, that at the time of delivery the increased fibrinolytic activity that occurs normally destroys the small amount of fibrin that can form in the uterus at the placental site.

A more plausible explanation for the hypofibrinogenemia, advanced by Weiner and his associates,[46] is that the fibrinogen is consumed by intravascular coagulation. This view is supported by the observation that intravenously injected fibrinogen disappears from the circulation with great rapidity.[47] Perhaps thromboplastic material, from the placenta, the dead fetus or the amniotic fluid, gains entrance to the maternal circulation. However, this hypothesis does not explain adequately the extraordinary constancy of the hypofibrinogenemia observed in 1 case (Fig. 3),

or the evenly progressive fall in the concentration of fibrinogen observed in 3 others (Fig. 4). No evidence that decreased synthesis of fibrinogen is responsible for the hypofibrinogenemia has been reported.

Jackson and his co-workers[24] have summarized reports in the literature of other changes in the clotting mechanisms that occurred in cases in which the fetus had died in utero. Four of 8 patients studied had thrombocytopenia; 10 of 11 had hypoprothrombinemia, usually of mild degree, and 1 had a diminished concentration of proaccelerin in her plasma. In our experience these changes have not been seen in patients with hypofibrinogenemia studied some days before delivery, and it is possible that they represent complications of the syndrome induced by the events of parturition. In 2 patients with hypofibrinogenemia whom we studied during delivery the transient marked thrombocytopenia reported by Hodgkinson, Margulis and Luzadre[25] was not observed.

The prognosis in patients with the hemorrhagic state associated with the retention of a dead fetus is good, although maternal deaths either from shock[48] or from lower-nephron syndrome[23] have been reported. Premature separation of the placenta has been described as a complication of the syndrome,[49] and may have been present in 1 of our patients.[47]

Prophylactically, patients in whom there is retention of a dead fetus should be warned to report any evidence of bleeding, however trivial. Determination of the fibrinogen concentration should be started in the third week after fetal death and should be repeated at weekly intervals even in the absence of hemorrhagic symptoms. If hypofibrinogenemia appears the defect should be corrected by the intravenous administration of 4 gm. of fibrinogen, repeated as often as necessary. While the concentration of fibrinogen is sustained in this way the uterus should be emptied as soon as one can do so. In our experience labor is not contraindicated even though it might be theorized that the pumping action of the contracting uterus might result in further entrance of thromboplastic material into the maternal circulation. Labor, either spontaneous or induced by oxytocin, was not accompanied by significant changes in plasma fibrinogen concentrations in 12 patients in whom the fetus had died in utero three to eleven weeks before, including 2 patients with untreated hypofibrinogenemia.[48,9]

The hypofibrinogenemia is corrected promptly by emptying of the uterus. In 2 patients in whom hypofibrinogenemia was known to exist before labor and delivery, fibrinogen promptly rose post partum even though no transfusions or injections of fibrinogen were given.

### Toxemia of Pregnancy

Pre-eclampsia and eclampsia are not ordinarily thought of as syndromes associated with hemostatic defects. Nevertheless, cutaneous hemorrhages are not unusual in this disorder, and bleeding into the central nervous system is a frequent terminal event. In recent studies it has been observed that hemostatic defects are common in patients with eclampsia or pre-eclampsia[50,51]; abnormalities have been detected in 29 of 31 patients. A few patients have epistaxes, gingival bleeding and cutaneous petechiae. The most frequent change observed in the laboratory has been a prolongation of the clotting time of a mixture of oxalated plasma and bovine thrombin. This abnormally long thrombin time lengthened as the pre-eclampsia increased in severity. Only a few patients were studied serially. In 2 such cases the abnormal thrombin time persisted for as long as eight weeks after delivery, long after the blood pressure and urine had become normal. Subsequently, the thrombin times returned to normal. The mechanisms responsible for the prolongation of the thrombin time are not understood, but the defect can be partially corrected by the addition of normal plasma from which fibrinogen, prothrombin, proconvertin and plasma thromboplastin component have been removed.

A second abnormality frequently noted in patients with pre-eclampsia or eclampsia is thrombocytopenia. Platelet counts between 26,500 and 108,000 were observed in 8 of 28 toxemic patients studied; 7 of the 8 had eclampsia. Of these 7, 3 had hemoglobinemia and hemoglobinuria, a combination described by Stahnke in 1911. It seems likely that the severe thrombocytopenia is an important factor in the genesis of cerebral hemorrhage in patients with eclampsia.

A third change observed has been prolongation of the clotting time of whole blood in silicone tubes, demonstrated in 19 of 27 patients; the significance of this finding is not clear. Although thrombocytopenia may be associated with a long clotting time in such tubes the prolongation was present in blood containing normal numbers of platelets. The abnormal thrombin time may have contributed to the long clotting time in silicone tubes, but in patients with abnormal thrombin times associated with other conditions, the clotting time in these tubes has not always been prolonged.

The pathogenesis of the hemorrhagic phenomena of pre-eclampsia and eclampsia is thus only beginning to be unravelled. The frequency of the abnormalities suggest that they may reflect mechanisms as basic to the disease as the classic symptoms of hypertension, albuminuria and edema. It is noteworthy that 17 of 27 patients also had evidence of a hemolytic state, including reticulocytosis, a falling hematocrit, hyperbilirubinemia and, in 3 cases, frank hemoglobinemia and hemoglobinuria. The combination of hemolytic anemia and thrombocytopenic purpura occurs in lupus erythematosus disseminata, but it was not possible to demonstrate positive L.E. tests in the 3 patients with frank hemoglobinuria. The possibility that some aberrant immunologic mechanism is re-

sponsible for pre-eclampsia and eclampsia, and for the hematologic abnormalities observed, is attractive, but no data other than a weakly and transiently positive direct Coombs test have been obtained to substantiate this view. Therapy for the hemorrhagic phenomena associated with toxemia of pregnancy is unsatisfactory. The administration of ACTH was without obvious benefit in 2 cases.

### Abortion

Attempts at self-induced abortion occasionally result in a fatal generalized hemorrhagic syndrome. Of 3 cases reported[24,52,53] hypofibrinogenemia was present in 2, and afibrinogenemia in the third. The platelet count was low in 2 patients, and the thrombin time, after due correction for the hypofibrinogenemia, was prolonged in 1. The pathogenesis of the hypofibrinogenemia was not elucidated; indeed, there is no reason to believe that the mechanism responsible was necessarily the same in all 3 cases. Two of the patients had concomitant bacteremia with gram-negative coliform bacilli,[24,52] but the organisms could not be shown to have fibrinolytic activity in vivo or in vitro. In 1 patient, who had taken menthol and camphor orally, there was acute yellow atrophy of the liver.[52] Although the hypofibrinogenemia was attributed to the hepatic damage, in retrospect this may have been a naïve view. In 2 cases[24,52] it was not possible to correlate the hypofibrinogenemia with abnormal plasma fibrinolytic activity. In the third, fibrinolytic activity was described, but the data reported are susceptible to other interpretations.[53] The 3 patients were subjected to intensive therapy without benefit. A priori, similar cases should be treated with intravenous fibrinogen, transfusion and antibiotics, after appropriate studies.

### Circulating Anticoagulants and Pregnancy

A rare group of syndromes, of great theoretic interest, are the hemorrhagic disorders associated with the presence in plasma of powerful abnormal anticoagulant substances. A number of such cases have been described in women in whom the first evidence of bleeding occurred within a few months of the termination of a pregnancy. In these patients the clinical picture is strikingly similar to that of hemophilia. Severe bleeding may occur into joints, soft tissues and the skin; there may be hematuria and increased menstrual bleeding. The clotting time of venous blood is greatly prolonged, despite a normal thrombin time and prothrombin time. A small amount of the patient's blood greatly prolongs the clotting time of normal blood, demonstrating the presence of a circulating anticoagulant. Dreskin and Rosenthal[54] and Conley and his associates[55] showed that the circulating anticoagulant in these patients inhibited the normal evolution of thromboplastic activity in shed blood. Treatment in such cases is unsatisfactory. Because of the presence of the anticoagulant the transfusion of normal blood will not correct the patients' coagulative defect, although this procedure may be needed to treat shock and to replace lost blood. Since the hemorrhagic symptoms may lead to considerable distress these patients wander from one hematologic center to another, and several have been described repeatedly, under a variety of diagnoses. Frick[56] believes that x-ray sterilization may have been responsible for a remission in symptoms that he observed in a woman with a circulating anticoagulant. However, in association with Dr. A. Weisberger, we have seen the apparently spontaneous disappearance of a circulating anticoagulant after a period of ten years in a woman previously described by Heinle et al.[57] Conversely, ovarian irradiation did not appear to benefit another patient with this disorder.[55] The pathogenesis is completely unknown, although several workers have suggested that an immune mechanism, in some way related to the fetus, is responsible.[54,56]

### Thrombocytopenic Purpura and Pregnancy

Pregnancy is occasionally complicated by thrombocytopenia. In some cases the decreased number of platelets is the result of idiopathic thrombocytopenic purpura or of sensitivity to such drugs as quinine and quinidine. The thrombocytopenia may also be an accompaniment of severe toxemia of pregnancy or some such disease as leukemia. Peterson and Larson[12] have recently reviewed the reported cases of thrombocytopenia in pregnancy. Of 41 patients who had thrombocytopenia at the time of delivery, 5 had increased post-partum bleeding. The maternal mortality, however, is low; only 1 of 48 mothers with thrombocytopenic purpura died (a patient described by Glick and Weiser who had a fatal hematemesis twelve days after a splenectomy performed in the sixth month of gestation). From the data currently available there is no reason to believe that the treatment of idiopathic thrombocytopenic purpura should differ in pregnant and nonpregnant patients.

### Other Causes of Bleeding during Pregnancy

One cannot infer that the conditions described encompass all the causes of bleeding in pregnancy, for cases will be seen that cannot be classified adequately. To cite one example, Lhoiry and Fayet[58] reported the case of a twenty-six-year-old woman in whom there was a delay in the separation of the placenta after the birth of the baby. Two hours post partum the placenta was delivered after an intramuscular injection of pituitary extract. She then bled repeatedly and died despite hysterectomy and transfusion; the blood was incoagulable. Finally, the report of a generalized bleeding state in association with the presence of an hydatidiform mole should be mentioned. The cause of bleeding under such conditions is not known.[59]

## Summary and Conclusions

Normal pregnancy is associated with an increase in the concentration of prothrombin, proconvertin and fibrinogen in the maternal plasma. During the course of delivery, no significant changes in the clotting mechanism have been found, but there is increased plasma fibrinolytic activity for several hours post partum. In some patients with premature separation of the placenta or amniotic-fluid embolism hypofibrinogenemia may develop acutely and may be associated with both uterine and generalized bleeding. The hypofibrinogenemia may be accompanied by thrombocytopenia, hypoprothrombinemia, proaccelerin deficiency and increased plasma fibrinolytic activity. The cause of the hemorrhagic phenomena in these two conditions is unknown. It is conjectured that thromboplastic tissue, from the placenta in premature separation, or from the amniotic fluid in amniotic-fluid embolism, enters the maternal circulation and causes intravascular coagulation, with subsequent defibrination. Treatment in both disorders should include intravenous injection of human fibrinogen and measures to combat shock. In premature separation of the placenta the uterus should be emptied, but preferably by vaginal delivery. In amniotic-fluid embolism, nonoperative therapy has been more effective than operative intervention in the control of bleeding.

A third cause of hypofibrinogenemia in pregnancy is the intrauterine retention of a dead fetus. In these cases fetal death usually occurs in the fourth month of gestation or later, and hypofibrinogenemia has been noted five or more weeks thereafter. At least in some cases the hypofibrinogenemia develops gradually. In others excessive bleeding at delivery has been the first evidence of hypofibrinogenemia. The mechanism responsible for the hypofibrinogenemia is unknown. Prophylactically, patients in whom there is intrauterine retention of a dead fetus should be studied frequently for evidence of bleeding or hypofibrinogenemia. Emptying of the uterus, after intravenous injection of human fibrinogen, corrects the defect promptly.

Severe pre-eclampsia and eclampsia are frequently accompanied by hemostatic defects, including prolongation of the clotting time of whole blood in silicone tubes, prolongation of the clotting time of mixtures of thrombin and oxalated plasma and thrombocytopenia. Neither the responsible mechanism nor therapy is understood.

Other, rarer causes of bleeding in association with pregnancy and parturition, including abortion, thrombocytopenic purpura and the appearance of circulatory anticoagulants, are discussed.

This study would not have been possible without the enthusiastic help of many obstetricians in Greater Cleveland. Human fibrinogen suitable for intravenous injection was provided through the generosity of the American Red Cross and the Cutter Laboratories, Berkeley, California.

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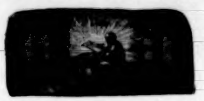
# MEDICAL INTELLIGENCE



## SEVERE BARBITURATE POISONING*

### Report of a Case

O. F. EHRENTHEIL, M.D.,† AND
W. E. MARCHAND, M.D.‡

BEDFORD, MASSACHUSETTS

THE successful management of a patient who had taken amobarbital (Amytal) in an amount considered almost always lethal is a gratifying experience. The case reported below is presented, however, to point out the importance of uninterrupted close supervision of the patient by a physician and to stress the fact that therapy must be closely gauged to the patient's everchanging condition.

Unique features of the case are as follows: the amount of barbiturate taken could be determined exactly; treatment could be initiated a relatively short time after ingestion of the drug; and the patient was observed constantly from the time of the ingestion of the drug. It is noteworthy that the total amount of medication given was unusually small as compared to that in reported cases of like severity, probably because treatment could be instituted early.

#### CASE REPORT

F.J.D., a 56-year-old man, had been in the hospital since 1938 because of a manic-depressive reaction, circular type. During the early years of his hospital stay he had exhibited suicidal tendencies but in recent years had been only overactive or depressed, clamoring frequently for his "pink lady" ("glycerite of Amytal").§ On occasion when very disturbed he was given this medication but mainly received a placebo.

On May 21, 1954, at 8:20 a.m., he found the door to the nurse's station unlocked, entered the room and smashed the glass of the medicine closet. Finding the bottle containing "glycerite of Amytal," he quickly gulped 332 cc. of the contents before he could be stopped by the psychiatric aide who had come to investigate the noise. As prepared in the hospital pharmacy, the 332 cc. of "glycerite of Amytal" contained 8.3 gm. of amobarbital, and since the patient weighed 50 kg., he had ingested 166 mg. of the drug per kilogram of body weight. The 332 cc. of "glycerite of Amytal" also contained 116.2 cc. of 95 per cent ethyl alcohol, an amount that was believed to have contributed significantly to the over-all severity of the central-nervous-system depression that subsequently appeared.

*From the Medical Service, Veterans Administration Hospital.
†Physician, Medical Service, Veterans Administration Hospital.
‡Chief, Medical Service, Veterans Administration Hospital.

§Formula:

| | |
|---|---|
| Amobarbital | 25.0 gm. |
| Ethyl alcohol (95%) | 350.0 cc. |
| Tr. sweet orange peel | 10.0 cc. |
| Amaranth (sol. 1%) | 0.3 cc. |
| Glycerine qs ad | 1000.0 cc. |

The salient features of the case, including the medication and supportive measures given, appear in Table 1.

#### DISCUSSION

A review of the literature shows that there is little agreement regarding what constitutes a fatal dose of Amytal Sodium taken orally. Several textbooks of pharmacology state that 3.0 gm. is generally fatal.[1-3] Cases of survival after much larger doses are reported by Koppanyi and Fazekas.[4] They collected 17 cases of treated amobarbital poisoning from the literature, and in only 1 case (with survival) was the dose of the drug taken larger than that in the case reported above.

By comparison with the doses mentioned in other reports it can be fairly stated that this patient took an extremely large amount of amobarbital, and yet his recovery was prompt with the unusually small total dosage of the therapeutic agents used. The prompt recovery is ascribed to the following factors: because the patient was in a hospital and was transferred to the Acute Medical Ward, therapy could be instituted within only thirty minutes of the time of discovery; the Acute Medical Ward was prepared to cope with such an emergency, having all the drugs ordinarily used in the treatment of barbiturate poisoning and other supportive agents at hand; and while general supportive and prophylactic measures were being given the main therapeutic effort was directed at combating the depressant action of the barbiturate on the central nervous system.

Our agent of choice in this regard was picrotoxin; 9.0 mg. was diluted up to 50 cc. with physiologic saline solution and given in amounts of approximately 5 cc. per minute until muscle twitchings developed, after which the injection was temporarily stopped. Our aim was to stimulate the central nervous system but not to the point of causing convulsions, which would have been deleterious to the patient since anoxia of varying degree is a constant feature during the convulsive state. Picrotoxin was used primarily for its effect on the medullary respiratory center and secondarily for its effect on the vasomotor center. Amphetamine sulfate, which is a satisfactory vasopressor agent when given parenterally, was administered to combat the impending circulatory failure in the early stages of treatment. In all stages this drug was used for its excellent stimulating action on the cerebral cortex.

Strychnine sulfate was given in the early stages of treatment primarily to counteract the depressant action of the barbiturate on the spinal cord and secondarily for its stimulant action on the respiratory and vasomotor centers.

Total dosage of analeptic drugs used were as follows: picrotoxin, 117 mg.; amphetamine sulfate, 100 mg.; and strychnine sulfate, 15 mg.

## Summary

The case of an inmate of a psychiatric hospital, who ingested 8.3 gm. of amobarbital and whose blood level of the drug was 4.12 mg. per 100 cc. is reported.

The management of the case and the drugs used in therapy are described.


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Table 1. *Treatment in a Case of Barbiturate Poisoning.*

| Time | Medication | | | Comment |
|---|---|---|---|---|
| | Picrotoxin | Amphetamine | Strychnine | |
| | mg. | mg. | mg. | |
| 21 May: | | | | |
| 0800 | | | | |
| 0830 | | | | Amobarbital (8.3 gm.) |
| 0840 | | | | |
| 0850 | | | | Patient very drowsy but resistive; gastric lavage attempted. |
| 0900 | | 20 | 10 | 40 gm. of magnesium sulfate in solution left in stomach. |
| 0910 | 9 | | | Deep coma; pulse thready; cyanosis; respirations 4 per minute. |
| 0920* | | 10 | | Respiration ceased; patient areflexic; oxygen & artificial respiration given. |
| 0930 | | | | 1000 cc. of 5% glucose in water given |
| 0940 | | | | |
| 0950 | 9 | | | Aspiration of mucus |
| 1000 | | | | Shallow gasps |
| 1010* | 9 | | | Patient breathing unassisted; respirations 16 per minute |
| 1020 | | | 5 | |
| 1030 | | | | Blood barbiturate level 4.12 mg. per 100 cc. |
| 1040 | | | | Patient responding to strong painful stimuli |
| 1050 | | | | |
| 1100 | 9 | | | |
| 1130 | | 10 | | |
| 1200 | 9 | | | |
| 1230 | | | | |
| 1300 | | | | Blood pressure 158/100; pulse 88 & respirations 16 per minute. |
| 1330 | | | | |
| 1400 | 9 | | | |
| 1430 | | | | Return of corneal reflexes |
| 1500 | | 20 | | 1000 cc. of 5% glucose in water given |
| 1530 | | | | |
| 1600 | | | | |
| 1630 | 9 | 20 | | |
| 2100 | 9 | | | 1000 cc. of glucose in water given |
| 2130 | | | | Patient moved extremities, turned head & opened eyes |
| 2330 | 9 | | | |
| 2400 | | | | Patient drowsy but easily aroused |
| 22 May: | | | | |
| 0030 | | | | |
| 0100 | 9 | | | |
| 0130 | | | | |
| 0430 | | | | |
| 0500 | 9 | | | Patient restless & tried to sit up |
| 0530 | | | | |
| 0830 | | | | |
| 0900 | | 20 | | Patient speaking |
| Totals | 99 | 100 | 15 | |

*Artificial respiration given between times indicated.

# EFFECT OF CARBONATED WATER ON GASTRIC ACID SECRETION*

LEON A. GREENBERG† AND JOHN McC. TURNER‡

NEW HAVEN, CONNECTICUT

THE effect of carbonated water on gastric functions has been a subject of numerous investigations. However, almost all of them have dealt with the effects of ingested carbon dioxide on the rate of gastric emptying[1-7]; very few have concerned gastric secretion.[8] Thus, although most of the data reported in the literature indicate that carbon dioxide generally causes a more rapid gastric evacuation, there is little and incomplete evidence about whether it causes an increased, decreased or unchanged secretion of gastric acid in response to a test meal.

The events of gastric activity after the ingestion of a meal are dynamic: as the rate of gastric secretion rises and declines gastric motility and consequent passage of the meal and secreted material into the duodenum are in continuous process. All these functions, furthermore, are causally related in some ways. Most of the methods described for studying the secretory activity of the stomach have been based on measurement of the acidity of the contents and the amount of acid present in the stomach at any given moment, as if these were synonymous with gastric acid secretion. They have ignored the necessity of knowing also the amount of secreted acid evacuated from the stomach if the total amount and the rate of acid secretion are to be accurately evaluated. Such an evaluation can be obtained only by simultaneous measurements of gastric evacuation.

Recently, a technic has been described[9,10] that makes possible the simultaneous estimation of the rate and quantity of gastric content evacuated and acid secreted, thus obviating the criticisms of the previous methods. In principle this procedure consists of the addition to the test meal of a known amount of phenol red, which is neither destroyed in nor absorbed from the stomach. The test meal itself consists of a material that is easily introduced and withdrawn from the stomach, does not undergo digestion in the stomach and provides an adequate stimulus to acid secretion but does not itself neutralize the acid. At any period after ingestion of such a meal the gastric content may be withdrawn by means of a stomach tube, and its volume, acid content and phenol red content measured.

From these measurements the amount of gastric contents evacuated from the stomach during this period may be calculated from the following relations:

The amount of phenol red leaving the stomach in any period (A) equals the amount present at the beginning of the period ($a_1$) less the amount present at the end of the period ($a_2$) — that is, $A = a_1 - a_2$.

The average concentration of phenol red leaving the stomach during the period (C) equals the concentration at the beginning of the period ($c_1$) in addition to the concentration at the end of the period ($c_2$) divided by 2 — that is, $C = \frac{c_1 + c_2}{2}$.

The volume of gastric contents leaving the stomach during this period (V) equals the amount of phenol red leaving the stomach divided by the average concentration — that is, $V = A/C$.

In similar fashion the amount of acid secreted during this period may be calculated from the following relations:

The amount of acid leaving the stomach during this time (a) equals the volume of gastric contents evacuated (V) multiplied by the concentration of acid at the beginning (C) in addition to the concentration at the end ($c_2$) divided by 2 — that is, $a = V \times \frac{c_1 + c_2}{2}$.

The amount of acid secreted during this period (A) equals the amount leaving the stomach (a) in addition to the amount present in the stomach at the end of the period ($a_2$) less the amount present at the beginning of the period ($a_1$) — that is, $A = a + a_2 - a_1$. The quantities $a_1$ and $a_2$ are the arithmetic product of the gastric volume and the concentration of acid at the respective times.

From these relations it can be readily seen that only from simultaneous quantitative knowledge of the rate of gastric emptying and acidity of the gastric contents can accurate information concerning the amount and rate of gastric acid secretion be obtained. The principles of this technic have been adopted in the present investigation to study the effect of carbonated water on the gastric acid secretion in human subjects.

## EXPERIMENTAL PROCEDURE

Ten healthy adult male subjects were used. The tests were started in the morning in a postabsorptive state, the subjects having fasted since the previous evening. A Levin tube was passed into the stomach, and 200 cc. of water swallowed to wash out the residual gastric contents. This fluid was rapidly withdrawn from the stomach and discarded. Each subject then drank, as quickly as he could, 400 cc. of a pectin test meal described by Hunt and Spurrell,[9] followed by 200 cc. of water on one occasion and 200 cc. of commercially prepared carbonated water on another. The completion of ingestion was taken as the zero time, and at fifteen, twenty, thirty, forty-five and sixty minutes after this time the total gastric contents were withdrawn, the volume measured, a

*From the Laboratory of Applied Physiology, Yale University.
†Associate professor of applied physiology and associate director, Laboratory of Applied Physiology, Yale University.
‡Research associate, Laboratory of Applied Physiology, Yale University.

small portion retained for determination of its phenol red and acid content, and the remainder immediately returned to the stomach. The concentration of acid in each sample withdrawn was measured by electrometric titration,[11] and the concentration of phenol red by the method described by Hunt.[12] From these data were calculated the amounts of gastric contents evacuated from the stomach and the amounts of acid secreted during each fifteen-minute period.

TABLE 1. *Amounts of Hydrochloric Acid Secreted during Various Periods.*

| SUBJECT | ACID SECRETED AT 0-15 MIN. | | ACID SECRETED AT 15-30 MIN. | | ACID SECRETED AT 30-45 MIN. | | ACID SECRETED AT 45-60 MIN. | |
|---|---|---|---|---|---|---|---|---|
| | WITH WATER | WITH CARBONATED WATER | WITH WATER | WITH CARBONATED WATER | WITH WATER | WITH CARBONATED WATER | WITH WATER | WITH CARBONATED WATER |
| | mg. | mg. | mg. | mg. | mg. | mg. | mg. | mg. |
| 1 | 201 | 216 | 228 | 136 | 135 | 27 | 46 | 9 |
| 2 | 216 | 204 | 211 | 126 | 112 | 24 | 49 | 5 |
| 3 | 198 | 189 | 222 | 125 | 126 | 29 | 48 | 10 |
| 4 | 214 | 208 | 198 | 151 | 108 | 14 | 30 | 3 |
| 5 | 221 | 212 | 224 | 139 | 122 | 22 | 38 | 4 |
| 6 | 197 | 204 | 211 | 124 | 127 | 29 | 50 | 13 |
| 7 | 215 | 222 | 226 | 135 | 118 | 30 | 46 | 8 |
| 8 | 202 | 196 | 213 | 134 | 110 | 15 | 32 | 3 |
| 9 | 217 | 219 | 209 | 115 | 125 | 31 | 44 | 7 |
| 10 | 207 | 204 | 219 | 132 | 115 | 23 | 39 | 5 |
| Mean | 210 | 207 | 216 | 132 | 120 | 24 | 42 | 7 |

The results of 80 such analyses carried out on 10 subjects are shown in Tables 1 and 2. Table 1 gives the amounts of acid secreted during each fifteen-minute period by the individual subjects with water and with carbonated water. Table 2 gives the mean values, for all the subjects, of the volume remaining in the stomach at the end of each fifteen-minute period and the volume evacuated and the amount of acid secreted during each of these periods with water and with carbonated water.

Several features are clearly and consistently apparent from these data. In the first place, from the volumes of gastric content found at the end of each fifteen-minute period and the calculated volumes evacuated during each period, the effect of carbonated water in hastening gastric emptying is obvious. The data also indicate that the major part of this effect of carbonated water is exercised during the first fifteen-minute period after its ingestion, when the concentration of carbon dioxide in the stomach is naturally highest.

Secondly, the total amount of acid secreted by the stomach in one hour after ingestion of the test meal is considerably greater with water alone than with carbonated water: 588 mg. of hydrochloric acid as compared with 370 mg. However, it is of interest that an insignificant difference in acid secretion between water and carbonated water occurs in the first fifteen-minute period when the mass of gastric contents is relatively large. But, since this mass diminishes in the subsequent periods to sufficiently smaller magnitudes more rapidly with carbonated water than with water alone, the rate of acid secretion is correspondingly diminished. These relations suggest that the ingestion of carbonated water does not directly influence the rate of secretion of acid by the gastric mucosa, that this rate is influenced largely by the relative volume of the gastric contents and that carbonated water lessens the total amount of acid secretion evoked by a test meal by hastening its evacuation from the stomach and thus attaining sooner a mass in the stomach that provokes less acid secretion.

Apart from any systemic physiologic implications of a greater or lesser gastric acid secretion the effects of carbonated water observed here in diminishing the duration and quantity of acid secreted suggest its value in counteracting any tendency toward gastric retention and subsequent increased acid secretion and so called "gastric hyperacidity."

TABLE 2. *Mean Values (All Subjects) for Recovery and Evacuation of Gastric Contents and for Secretion of Hydrochloric Acid after Ingestion of Water and Carbonated Water.*

| TIME OF WITHDRAWAL | AFTER INGESTION OF WATER | | | AFTER INGESTION OF CARBONATED WATER | | |
|---|---|---|---|---|---|---|
| | VOLUME OF GASTRIC CONTENTS RECOVERED FROM STOMACH | VOLUME OF GASTRIC CONTENTS EVACUATED | ACID SECRETION OF GASTRIC CONTENTS | VOLUME OF GASTRIC CONTENTS RECOVERED FROM STOMACH | VOLUME OF GASTRIC CONTENTS EVACUATED | ACID SECRETION OF GASTRIC CONTENTS |
| min. | cc. | cc. | mg. | cc. | cc. | mg. |
| 15 | 432 | 228 | 210 | 340 | 318 | 207 |
| 30 | 306 | 162 | 216 | 187 | 190 | 132 |
| 45 | 228 | 108 | 120 | 101 | 110 | 24 |
| 60 | 146 | 90 | 42 | 31 | 82 | 7 |

## CONCLUSIONS

Carbonated water hastens gastric emptying of a test meal.

Carbonated water does not itself directly influence the rate of acid secretion in the stomach but, through more rapid gastric evacuation of a test meal, causes a diminished total secretion of acid.

Relief from gastric retention and subsequent "hyperacidity" may be afforded by this effect of carbonated water.

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# CASE RECORDS
## OF THE
# MASSACHUSETTS GENERAL HOSPITAL

**Weekly Clinicopathological Exercises**

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

## CASE 41291

### PRESENTATION OF CASE

A seventy-one-year-old retired accountant entered the hospital complaining of indigestion.

Fifty years before admission while in Puerto Rico the patient had a "tropical complaint" characterized by indigestion and midepigastric distress. Since that time at irregular intervals he had experienced attacks of postprandial epigastric distress. These came on almost immediately after meals, were not related to any particular food, to position or to exertion but did follow excessive eating and drinking of alcohol. Relief was obtained by fasting or dieting or by abstaining from alcohol. There was no associated nausea, vomiting or melena. He never consulted a physician or took medicine. Two or three months before entry the distress became more severe and frequent to the point where it occurred after every meal and sometimes lasted until the next one. It was gnawing in nature, and did not radiate. He was treated by his family physician with a bland diet, belladonna and "white tablets" with only temporary relief. A gastrointestinal series and two barium-enema examinations were said to have been negative. Three stool benzidine tests were positive. His appetite declined markedly, and he became progressively weaker. During the six months before admission he lost 55 pounds. Shortly before admission the pain became unremitting, and partial relief was obtained only by lying down. With the recent increase in pain the patient noted the onset of slight itching of the back, which was not accompanied by jaundice or a rash. It gradually increased in intensity so that it interfered with sleep.

The patient admitted to having consumed as much as 1 pint of whisky a day in the past, but now limited the intake to ½ pint a week.

The temperature was 98.6°F., the pulse 80, and the respirations 18. The blood pressure was 110 systolic, 60 diastolic.

Physical examination revealed a small, alert, cachectic man. The chest was increased in anteroposterior diameter and was hyperresonant; expirations were prolonged. The heart sounds were distant and a Grade 1 apical systolic murmur was heard at the apex. The liver was palpable 3 fingerbreadths below the right costal margin. Its edge was slightly tender, firm and smooth. The prostate was slightly enlarged and firm. There was phlebitis and edema of the left leg.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 11.8 gm. per 100 cc. and a white-cell count of 13,100, with 48 per cent neutrophils, 6 per cent lymphocytes, 4 per cent monocytes and 42 per cent eosinophils. The cephalin and the thymol flocculation tests were negative. The alkaline phosphatase was 3.4 units per 100 cc. The bilirubin

FIGURE 1. *Posteroanterior View of the Barium-Filled Stomach and Upper Portion of the Small Bowel. There is irregularity of the most proximal portion of the jejunum and another zone 10 cm. distal to it (arrows).*

was less than 0.2 mg., the total protein 4.7 gm., the albumin 2.8 gm., and the globulin 1.9 gm. per 100 cc. A glucose tolerance test showed a fasting blood sugar of 123 mg., a thirty-minute level of 150 mg., a sixty-minute level of 195 mg. and a two-hour level of 162 mg. per 100 cc. A blood Hinton test was negative. An x-ray film of the chest revealed the presence of multiple healed fractures in the posterior rib cage on the left. The lungs were emphysematous and had increased linear markings, especially in the region of the right middle lobe. The heart was not enlarged. A Graham test was negative. A gastrointestinal series demonstrated a normal esophagus, stomach and duodenum. There was no delay in gastric emptying. In films made directly after the barium meal there was some irregularity of the jejunum over a 5-cm. segment just distal to the ligament of Treitz, then an intervening 10-cm. zone of relatively normal-appearing small bowel followed by another segment that was somewhat irregular in outline (Fig. 1).

An operation was performed on the sixth hospital day.

## Differential Diagnosis

Dr. Daniel S. Ellis*: This elderly man had gastrointestinal symptoms for fifty years, but in the year before admission he had a definite change in symptoms, with weakness, anorexia, weight loss and a severe, unremitting pain. The only findings on physical examination that may be of importance other than the cachexia are the hyperresonance of the chest and the enlargement of the liver. I am going to say that he had emphysema and that that was the only significant disease in the chest unless Dr. Hanelin shows me evidence of other disease in the films. The liver apparently was not very large; in a cachectic man with an emphysematous chest a liver palpable 2 or 3 fingerbreadths below the right costal margin would not be unusual, and I have no other evidence of its enlargement. There was no mention of nodularity of the liver. I was given three x-ray films of the abdomen with the protocol, and I am not impressed by the enlargement of the liver in these films. Another point in the history, which may be very important, is the pruritus.

The important laboratory findings are the occult blood in the stools, the slight anemia and the marked eosinophilia. The last finding is one on which I have relied heavily in making a diagnosis.

From the symptoms and physical findings I believe this patient had a malignant neoplasm of some kind. There was a lesion or multiple lesions in the small bowel; the problem is to determine what kind of neoplasm this man had in the small intestine and whether or not any disease in addition to that was demonstrated on the x-ray films. After looking over the literature last night I find that I am fortunate in having an expert on the roentgenologic diagnosis of diseases of the small bowel in the person of Dr. Hanelin,[1] who will interpret the films for us. Perhaps he can make the diagnosis for me. Is there anything in the chest, Dr. Hanelin, or can I dismiss that?

Dr. Joseph Hanelin: The lungs are emphysematous, and that is about all we can say. The heart is not enlarged; there may be some fullness of the left ventricle. There are old rib fractures on the left side.

Dr. Ellis: Are those fractures traumatic fractures that have healed?

Dr. Hanelin: Yes; I see no evidence of any pathologic bone involvement. I should agree with Dr. Ellis that there is no enlargement of the liver or spleen and think, as he does, that the emphysema probably allowed the liver to be readily palpated. The stomach and duodenum are normal. The abnormalities are in two segments of small intestine — one immediately beyond the ligament of Treitz and another about 10 cm. beyond it of similar length (Fig. 1). A complete small-bowel examination was not done. Certainly, the first condition that comes to mind is neoplasm. I think I shall let Dr. Ellis speculate about the type since this is really not an x-ray discussion.

Dr. Ellis: Obviously, the final diagnosis of this lesion can only be made by a biopsy. I have already committed myself by saying that, because of the marked weight loss, progressive weakness, anorexia, anemia and the steady downhill course over the months immediately preceding admission, I think that this was a malignant neoplasm. Before discussing the kind of neoplasm, however, I think I should mention other possibilities.

There are several "red herrings" in the protocol. In the first place I am shifted off on a tangent by the intimation that the patient had lived in the tropics and that he had eosinophilia; immediately, the question comes up, Was there parasitic involvement? I am not familiar with any parasitic disease that might give this x-ray picture. I do not think hookworm will do it. Nor do I think schistosomiasis will, but I have not seen enough x-ray films of schistosomiasis to know. Judging by what I have read I should consider that an unlikely possibility. I am told that there are gastrointestinal lesions of eosinophilic granuloma. I do not think I should do any more than mention it. Amebiasis may rarely be associated with eosinophilia. Amebiasis, when it involves the gastrointestinal tract, is most commonly localized in the cecal region. I am not aware of the possibility of amebic granulomas high in the small bowel. The other granulomatous diseases like regional enteritis and tuberculosis should be mentioned. It would be most unusual for a tuberculous lesion in the jejunum to look like this. The lesions of regional enteritis seem to me to be slightly different. Perhaps Dr. Hanelin would be willing to tell us why he thinks this may not have been regional enteritis.

Dr. Hanelin: This does not look like any regional enteritis that I have ever seen. It is unusual, of course, to see regional enteritis in this location, although rarely it may involve the uppermost portion of the gastrointestinal tract.

Dr. Ellis: Regional enteritis has involved the

*Assistant physician, Massachusetts General Hospital.

duodenum and jejunum, but I think the configuration here is not that of regional enteritis.

DR. HANELIN: I should expect to see narrowing of the bowel and frank evidence of ulceration but not quite so much irregularity.

DR. ELLIS: Also, there was no history of the patient's having had a great deal of diarrhea; I think he would have had some diarrhea with regional enteritis of a severity that made him so ill. These are the possibilities besides neoplasm that I should consider, but I believe that neoplasm is more likely.

What kind of neoplasm was this? Five per cent of all gastrointestinal malignant neoplasms are located in the small bowel. Botsford and Sibel,[2] several years ago, reported 65 cases of small-bowel tumor, of which 33 were malignant; of those 33, 18 were adenocarcinomas, 13 were lymphosarcomas and 2 were argentaffinomas. I think everyone will concede that carcinoma is more likely in this area than any other type of neoplasm, although it may be only slightly more common than lymphoma. Now I shall go back to two findings that I mentioned previously — namely, the eosinophilia and the generalized pruritus, both of which are common in lymphomatous disease. Eosinophilia is also seen with hepatic neoplasms. The liver-function tests were negative, there was no evidence that the liver was greatly enlarged, and it was certainly not nodular, so that I shall dismiss metastatic neoplasm to the liver as the cause of the eosinophilia. That leaves lymphoma. There are several different kinds of lymphoma, and by and large it lies in the realm of the pathologist to tell us which kind was present. There are, however, some clues that point to one kind of lymphoma rather than the other. The generalized itching and the eosinophilia, I am told, are seen more often with Hodgkin's lymphoma than with the other types so I might narrow this even further. Jackson and Parker[3] state that Hodgkin's paragranuloma never occurs in the gastrointestinal tract. Hodgkin's granuloma probably is the most common type of lymphoma. I should be inclined to believe that this was probably the type in this case but for the fact that there were multiple lesions. In the series of diseases in the small bowel reported by Jackson and Parker[3] there were no cases of Hodgkin's granuloma manifesting themselves as multiple lesions; they are usually single lesions in the gastrointestinal tract from disease elsewhere. Hodgkin's sarcoma, on the other hand, as frequently as not, produces multiple lesions in the gastrointestinal tract. Therefore, I am going to say that this patient had a malignant lymphoma of the jejunum and that since there were multiple lesions he most probably had Hodgkin's sarcoma rather than Hodgkin's granuloma.

I should mention one other possibility because of the multiple lesions — that is, carcinoid. That is more likely to be found in the region of the cecum and small bowel; however, it is found in the upper small intestine occasionally.

DR. WILLIAM H. BAKER: I thought that eosinophilia was not usually associated with amebiasis; I thought that was one major distinguishing feature.

DR. ELLIS: It is much less likely than with the other parasites.

### CLINICAL DIAGNOSIS

Metastatic malignant process of small bowel.

### DR. DANIEL S. ELLIS'S DIAGNOSIS

Hodgkin's sarcoma of small bowel.

### ANATOMICAL DIAGNOSIS

*Malignant lymphoma, reticulum-cell-sarcoma type, of small bowel.*

### PATHOLOGICAL DISCUSSION

DR. AUSTIN L. VICKERY: Dr. McDermott, would you outline the operation that you performed on this man?

DR. WILLIAM V. MCDERMOTT: When we opened the peritoneal cavity we saw a series of tumor masses beginning at the ligament of Treitz and involving most of the small bowel through its entire extent. There must have been at least a dozen lesions of varying sizes up and down the small bowel. The mesentery contained many large lymph nodes, including a mass of lymph nodes around the superior mesenteric vessels. We believed that the primary tumor was a lymphoma; it had a typical rubbery consistence. None of the tumor extended through the serosa at the time of operation. We debated how best to determine the diagnosis. Finally, we selected a large lymph node, which we thought the pathologist would tell us had the characteristic picture of lymphoma. No surgical resection was possible.

DR. VICKERY: The lymph-node biopsy obtained at the time of exploration showed only chronic lymphadenitis on microscopical examination. The node was large and suggestive of lymphoma on cut surface, but when the gastrointestinal tract is involved with malignant lymphoma, biopsy of enlarged mesenteric lymph nodes has often proved to be a diagnostic trap. This patient was referred to Dr. Milford D. Schulz for x-ray treatment. I think it is interesting that in the record Dr. Schulz has dictated a note to the effect that he gave a good deal of weight to the two observations that Dr. Ellis mentioned — the itching of the skin and the eosinophilia — as favoring the diagnosis of lymphoma.

After a postoperative course of x-ray therapy the patient was fairly well for a while and then proceeded to go rapidly downhill and died six weeks after laparotomy.

Post-mortem examination showed multicentric intestinal tumor masses, rubbery in consistence, irregular in outline and intramural in location extending from the ligament of Treitz down the jejunum for a distance of 80 cm. There was a generalized peritonitis, and the peritoneal cavity contained a liter of purulent fluid. The opened bowel revealed focal mucosal

ulcerations, corresponding to zones of tumor infiltration and necrosis (Fig. 2). One of these ulcerated areas had perforated through the bowel wall, producing the peritonitis.

On microscopical examination these tumor masses proved to be malignant lymphoma. The pleomorphism and cytology of the neoplasm suggested a classification in the reticulum-cell-sarcoma group.

FIGURE 2

We wondered if the x-ray therapy and the resultant tumor reaction were not responsible for the extensive necrosis in the tumor; this has been described in the radiology literature.[4] Seventy-nine cases of primary malignant lymphoma of the gastrointestinal tract were reported last year by Allen et al.[5] from the files of this hospital covering a forty-year period. Twenty-five of these occurred in the small bowel. The authors pointed out the high relative incidence of malignant lymphoma to all forms of malignant small-bowel neoplasms, lymphomas comprising about 40 per cent of the total. This figure is in striking contrast to other portions of the gastrointestinal tract (Fig. 3).

It is worth while pointing out that, although very frequently the regional lymph nodes are enlarged with primary lymphoma of the gastrointestinal tract, they are not necessarily involved by the tumor. Approximately half the cases of malignant lymphoma of the small bowel in this series that had resections did not show lymph-node involvement. The warning and, of course, the lesson to be learned is that the primary lesion, not the lymph node, should be biopsied. Multicentric tumors are not uncommon in lymphoma of the small bowel and made up about 25 per cent in this series of cases; these cases proved to have a prognosis about 50 per cent worse than those with single lesions. Fifteen patients with small-bowel

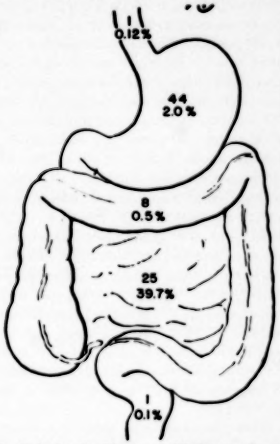


FIGURE 3. *Relative Incidence of Malignant Lymphoma to All Malignant Tumors of the Gastrointestinal Tract, Massachusetts General Hospital, 1913-1953 (Reproduced from Allen et al.[5] with the Permission of the Publisher).*

lymphoma had resections; 5 of these had a five-year survival. The majority of the patients died within a year, so that the prognosis in general is not good, but it is better than that for carcinoma of the small bowel.

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## CASE 41292

### PRESENTATION OF CASE

A fifty-year-old wine merchant entered the hospital because of epigastric pain and vomiting.

Three days before admission the patient went on a drinking spree and fell down on numerous occasions.

One day later he noted bright-red blood in the urine but had no other urinary symptoms. On the day before admission, after striking his nose, he had intermittent epistaxes. On the day of entry midepigastric pain appeared insidiously and was accompanied by the vomiting of brownish-black blood on several occasions. The patient was able to void only a little bloody urine. Lower abdominal pain subsequently developed. The epigastric pain at times shifted to the right flank and at other times radiated directly through to the back. There was no history of melena. However, since the day before admission there had been no passage of feces or gas by rectum.

The patient had been a heavy drinker for twenty-five to thirty years. However, he claimed that he had not drunk alcohol for two years until the present bout. For a twenty-year period he had had abdominal discomfort. X-ray films had been taken "many times" to rule out ulcer and gallstones; all were said to have been normal, and he was told that he had a "nervous stomach." The last negative gastrointestinal series was three years before admission. There was an episode of hematuria of one day's duration three years before entry, but there had been no recurrence since. Two months before admission the patient said that he was pronounced healthy after examination in a medical clinic.

Physical examination revealed an acutely ill, tremulous, heavy-set man complaining of abdominal pain and groaning whenever moved. There were numerous ecchymoses over the body, including the right eye and the nose. There were no spider angiomas or liver palms. Examination of the chest was negative. The abdomen was generally tender and spastic but not rigid. The chief areas of tenderness were the midepigastric and suprapubic regions. There were rebound tenderness referred locally and some tenderness in the right costovertebral angle. Peristalsis was present but hypoactive. Rectal examination was negative. There was no peripheral edema.

The temperature was 101°F., and the pulse 100. The blood pressure was 150 systolic, 90 diastolic.

Urinalysis revealed a grossly bloody urine, a specific gravity of 1.021, an olive glucose test, a trace test for diacetic acid and a negative test for bile. The sediment was loaded with red cells. Examination of the blood showed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 21,700, with 82 per cent neutrophils. The platelets appeared normal, and the red cells were normocytic and normochromic on the smear. The prothrombin time was normal. The serum amylase was 24 Russell units, the bilirubin 1 mg., and the nonprotein nitrogen 75 mg. per 100 cc.; the sodium was 136 milliequiv., the potassium 4.6 milliequiv., the carbon dioxide 20 milliequiv., and the chloride 100 milliequiv. per liter. A guaiac test on the stool was negative. A sample of grayish, watery gastric contents showed a + guaiac reaction and a negative Töpfer reaction. An x-ray film of the chest demonstrated elevation of the diaphragm, transverse position of a normal-sized heart and linear atelectasis above the right leaf of the diaphragm. Beneath the right leaf of the diaphragm there was a radiolucent area, which appeared to have a fluid level. Upright and supine films of the abdomen showed gas-filled, dilated loops of small bowel on the left side. Gas and fecal material were visible in the colon. The visceral and soft-tissue shadows were not remarkable.

A Foley catheter was inserted into the bladder. A few clots were evacuated, and there was intermittent drainage of grossly bloody urine thereafter.

Four hours after admission the abdomen was noted to be more tender. Tenderness was still chiefly in the epigastrium and right flank but was now also present in the right lower quadrant. Peristalsis was absent, and the abdomen was becoming quite distended. The pulse was now 120. The patient received transfusions and antibiotics and was taken to the operating room seven hours after admission.

## Differential Diagnosis

Dr. Glenn E. Behringer*: May we see the x-ray films?

Dr. Joseph Hanelin: The films of the chest are normal except for the elevated diaphragm. The radiolucent areas described below the uppermost portion of the right leaf of the diaphragm certainly raise the question of free intra-abdominal air. One, however, would like to confirm that by an additional view. The upright and supine films of the abdomen reveal multiple, moderately distended, gas-filled loops of small bowel on the left side. There is also gas and fecal material in the colon, most of which lies in the transverse portion although some gas is seen in the cecum and rectum. The psoas-muscle shadows are sharply demarcated. If there is any increase in intra-abdominal fluid it is very slight, for I do not see any evidence of it. The liver and spleen appear normal in size.

Dr. Behringer: This case presents evidence in the history, physical examination, laboratory tests and x-ray films of disease in at least two organ systems — the urinary and the gastrointestinal tracts. I thought, as I read the protocol, that perhaps the best way to discuss this problem was to consider the patient's condition on admission to the hospital. He was acutely ill and febrile, with a tender abdomen, which gave classic signs of peritoneal irritation. The x-ray films revealed what was interpreted as and appeared to be air beneath the diaphragm, and ileus. He had a leukocytosis. During the four hours after admission the abdominal signs progressed, tenderness appeared in the right lower quadrant, and the pulse rose. I think that these facts can be interpreted to indicate that the patient had a fulminating and advancing peritonitis, presumably from a ruptured viscus. The urinary tract must also be considered. The patient gave a history of hematuria on one occasion three years before admission but had no further symptoms

*Assistant in surgery, Massachusetts General Hospital.

of urinary-tract difficulty until the present episode, which began after a series of falls. The laboratory findings of interest are the negative Töpfer reaction and the positive guaiac tests on the gastric fluids, the elevated nonprotein nitrogen, the sugar in the urine and the slight elevation of the serum amylase.

In order to interpret these facts one must speculate about the various conditions that lead to generalized peritonitis from a ruptured viscus and urinary-tract bleeding. The ingestion of toxic substances — methanol, for instance — causes gastritis and renal damage; it may even cause hematuria with clots. However, this patient did not present the picture of methanol intoxication, and the appearance of the hematuria forty-eight hours before admission, before any gastric symptoms or abdominal symptoms were noted, is not appropriate.

He gave a history of abdominal discomfort for twenty years and had been investigated many times for ulcers and gallstones so that the symptoms must have been upper abdominal and suggestive of disease in the stomach, duodenum or biliary tract. The fact that several series of x-ray examinations failed to demonstrate a gastric or duodenal ulcer does not rule it out, especially since the symptoms continued.

About the urinary tract, I am told that he had an episode of hematuria three years before admission. I doubt if this fact is of significance in relation to the present situation. The hematuria in a man of this age, if it was terminal in nature, was probably due to prostatitis. The hematuria on admission was probably caused by the trauma from the falls, which must have been severe since he had "numerous ecchymoses over the body, including the right eye and the nose." From the nature of the hematuria—that is, the gross blood in the urine noted by the patient, and also on catheterization in the Emergency Ward — and the presence of right-costovertebral-angle tenderness I should think that he probably had a traumatic laceration of the right kidney.

In reconstructing the sequence of events leading up to admission to the hospital I should visualize the following: three days before admission the patient had fallen on numerous occasions and suffered lacerations of the right kidney, which were manifested by hematuria. He apparently kept up the alcoholic intake, for the next day he struck his nose hard enough to cause it to bleed. On the day of admission an abdominal catastrophe of some sort occurred; it caused epigastric, right-flank and suprapubic pain, which radiated to the midback and was later noted in the right lower quadrant. This catastrophe was associated with the vomiting of brownish-black material that was guaiac positive. This was interpreted as peritonitis due to a rupture of a perforated viscus. The location of this perforation could well be the duodenum or cecum since these organs are known to rupture with trauma when they are distended. A perforated appendix and perforated diverticulum of the cecum are remote possibilities. I believe, however, that a perforated duodenal or gastric ulcer is a better possibility in view of the fact that the episode occurred during an alcoholic spree. Gastric rather than duodenal ulcer is probably a better possibility since on at least one occasion there was no free hydrochloric acid in the stomach.

With the development of the peritonitis, epigastric pain and right-flank pain from the leakage of the gastric or duodenal contents, he became febrile, severely ill and dehydrated, and vomited. The vomiting could explain the elevated nonprotein nitrogen since the right kidney with its pelvis full of blood clot was nonfunctional and in the dehydrated state of the patient the remaining kidney was not able to maintain normal excretion. I believe that a latent diabetes, which was not discovered in the examination three years before admission, revealed itself by glycosuria under the conditions of starvation, dehydration and stress. An elevated serum amylase is not infrequently seen with the peripancreatitis associated with a generalized peritonitis.

My diagnoses, then, would be traumatic laceration of the right kidney, peritonitis due to perforated viscus, probably a gastric ulcer, with leakage down the right gutter, and diabetes mellitus.

DR. RICHARD FIELD: I wonder what Dr. Behringer thinks of the possibility of a perforation of the urinary bladder as a basis for both the peritonitis and the hematuria?

DR. BEHRINGER: That is possible, although I think a fairly remote possibility, since the patient had no pain with the initial hematuria; for forty-eight hours afterward he had hematuria without pain and continued to pass urine, although in small amounts. Secondly, it would not account for the presence of air under the diaphragm, and thirdly the symptoms, being upper abdominal in onset, would not be in favor of a ruptured bladder and peritonitis from intraperitoneal urine, with which I think the initial pain is lower in the abdomen.

### CLINICAL DIAGNOSES

Perforated gastric ulcer.
Peritonitis, generalized.

### DR. GLENN E. BEHRINGER'S DIAGNOSES

Laceration of right kidney.
Peritonitis, from ruptured gastric ulcer.
Peripancreatitis.
Diabetes mellitus.

### ANATOMICAL DIAGNOSIS

*Ruptured urinary bladder, with peritonitis.*

### PATHOLOGICAL DISCUSSION

DR. ROBERT E. SCULLY: The patient was operated on by Dr. Waddell.

DR. WILLIAM R. WADDELL: About 2000 cc. of blood and urine was found within the peritoneal

cavity. The stomach, the duodenum, the gall bladder and the colon were normal. A large rupture admitting one finger was found in the urinary bladder. This was sutured with three layers of interrupted catgut. The tear was in the dome of the bladder — that is, what I assume to have been the dome of the distended bladder. It was a ragged tear, about 2 cm. long and was easy to identify by palpation. It was rather easy to repair; after the edges were trimmed, they were approximated and infolded, and a suprapubic cystotomy was created at the free vesical space. An unusual point about this case is that it is one of the few cases that have reached clinicopathological-conference status without a single piece of pathological tissue.

DR. BEHRINGER: How do you account for the free air under the diaphragm, Dr. Waddell?

DR. WADDELL: That probably was introduced in the Emergency Ward during catheterization and irrigation of the bladder, in an attempt to remove blood clot. The situation is somewhat analogous to the air that sometimes appears in the pleural space after thoracentesis.

DR. HANELIN: In that case one has to assume that the laceration was free in the peritoneal space.

DR. WADDELL: I think it was a free perforation into the peritoneal cavity.

DR. FARAHE MALOOF: Was all the irrigation fluid recovered?

DR. WADDELL: I do not think so. The inability to recover all the fluid was not wholly disregarded by everyone who saw this patient. Dr. Kleaveland brought up the possibility of a perforated bladder preoperatively. This particular fact was not appreciated altogether, however.

DR. HANELIN: How much fluid was present?

DR. WADDELL: The 2000-cc. bottle was filled with the aspirate from the abdominal cavity.

DR. HANELIN: Was most of the fluid out of the pelvis?

DR. WADDELL: The whole abdominal cavity was filled with fluid.

DR. HANELIN: That is interesting. I should think that this amount of fluid, particularly within the true pelvis, unless it had accumulated after the x-ray film was taken, would have been more evident on the film; I do not see any indication of free fluid in the pelvis or abdomen.

DR. WADDELL: Actually, there was more than 2000 cc. because a large amount of fluid went into the operating-field drapes.

DR. HANELIN: Do you recall when the films were made — before or after the catheterization of the bladder?

DR. WADDELL: I do not know.

DR. HANELIN: What is the likelihood of the films having been made first and of the fluid having been introduced at the time irrigation of the bladder was attempted?

DR. WADDELL: I cannot answer that.

DR. RICHARD N. KLEAVELAND: Would you reconstruct how this tear arose?

DR. WADDELL: I think the trauma superimposed on increased intravesicular pressure ruptured the bladder. The patient was covered with bruises — a black eye, and ecchymoses in various other places over the body. The people who knew him said that he had fallen on numerous occasions during his alcoholic bout the preceding day.

DR. BENJAMIN CASTLEMAN: When did the tear occur? Three days before admission or just before he came in?

DR. WADDELL: I do not believe the tear had been present for three days although I really do not know when it occurred. The status of the rupture in the bladder indicated that it was more than just a few hours old, for the hemorrhage was dark, which makes me think that the bladder ruptured the day before admission.

He made an uneventful convalescence. Urine in the peritoneal cavity seems to excite a great deal less reaction, as judged by ileus and so forth, than intestinal contents from a perforated duodenal ulcer do. The peristaltic activity returned within forty-eight hours, and he convalesced normally.

DR. CASTLEMAN: On antibiotics?

DR. WADDELL: He received multiple antibiotics.

DR. BEHRINGER: It is surprising that a man could have hematuria for three days and have that much urine in the abdominal cavity and yet only have pain on the day of admission.

DR. CASTLEMAN: I suppose that it is possible that trauma to the kidney caused the hematuria three days before admission.

DR. WADDELL: It is possible, but it does not seem very likely because we inspected the kidneys as carefully as we could and found no leakage of blood in the retroperitoneal tissue.

DR. BEHRINGER: Did he have any hematuria after the operation?

DR. WADDELL: Yes; he had hematuria for several days, but he had a new wound in the bladder in addition to the old wound.

The history is clouded by the fact that the patient was quite neurotic and had been investigated many times in the past for upper abdominal complaints that some physicians thought were caused by gall-bladder disease.

DR. JOHN T. QUINBY: What was the explanation for the vomiting of blood?

DR. WADDELL: Gastritis, I assume.

DR. SCULLY: According to some of the medicolegal literature rupture of the urinary bladder in persons who have been drinking is a well recognized event even though it is rare. It is stated in the literature* that only a slight amount of trauma is necessary to rupture these distended bladders. The rupture, as in this case, is characteristically in the dome of the bladder.

*Gonzales, T. A., Vance, M., Helpern, M., and Umberger, C. J. *Legal Medicine: Pathology and toxicology.* Second edition. 1349 pp. New York: Appleton, 1954. Pp. 255-258.

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## GOVERNOR'S MESSAGE

THE address delivered on May 18 by Governor Herter at the annual dinner of the Massachusetts Medical Society and published elsewhere in this issue of the *Journal* reveals an unusual understanding by the present administration of the problems of public health.

Two characteristics of federal and state relations in regard to matters of health are of the times. They represent a willingness if not, indeed, an eagerness on the part of a majority of the voters to cast their burdens on their government. A third characteristic, as Governor Herter sees it, is a salutary one, consisting of a determination by many authorities that private physicians shall be utilized in providing the health services that federal and state governments are financing.

True insight is shown in the final paragraph of His Excellency's address. Here he defines the real challenge of the future as that of assuring to governmental procedures sufficient elasticity so that Government can keep abreast of the progress being made by scientific medicine.

A sympathy with scientific progress in medicine may be considered as part of Governor Herter's heritage, for he is the nephew and namesake of Christian Archibald Herter, a graduate in medicine from Columbia University in 1886. Dr. Herter, founder of the Herter Lectures at Johns Hopkins University and Bellevue, founded also, in 1905, with Professor J. J. Abel, the *Journal of Biological Chemistry* and became its editor.

## THE ASIA FOUNDATION

THE term "international bridge," whether of health or of understanding in general, has become so popular in the decade since the war as to run some danger of losing its true import. The facts to remember are that these bridges must be created wherever the need for them exists, that the traffic over them must be on the soundest cultural levels, and that it must not flow too long in one direction alone.

The first bridges that were developed to this continent came naturally from the east, and over them poured for some time the culture of the Old World. Tardily, the two Americas set to the spanning of the gulf between them, and finally an increased understanding with the reawakened countries of Asia is taking place. The determination on both sides of the world is that the Asian renaissance will be like nothing that the great continent has yet known; that wherever normal intercourse with the West is permitted the resulting benefits shall be diffused to all the people at every level.

For many centuries, since their ancient cultures lost impetus, the populations of the great land mass that is Asia have lain partly dormant, unaware of

their potentialities in a modernizing world, the accessible region of their continent exploited by western commerce and western colonialism and with much of its population the victims of oppression and corruption from within. As Asia regains independent life and renewed vigor it is essential for world welfare that it should share in the benefits of western progress and be inoculated with the principles of democracy.

To this end the Asia Foundation, a nonpolitical, nonprofit organization was established in San Francisco in 1951 as the Committee for Free Asia. Its purposes, as set forth in its articles of incorporation, are:

a. To make private American support available to individuals and groups in Asia who are working for the attainment of peace, independence, personal liberty, and social progress.

b. To encourage and strengthen active cooperation, founded on mutual respect and understanding, among voluntary organizations — Asian, American, and international — with similar aims and ideals.

c. To work with other American individuals and organizations for a better understanding in the United States of the peoples of Asia, their histories, cultures, and values.

Believing in the part that spontaneous action by private citizens must play in the functioning of democratic societies, the Foundation seeks to achieve its aims by privately aiding those "who are promoting the manifold aspects — spiritual, civic, economic, artistic, social and educational — of the Asian renaissance." It believes in the right of Asian peoples to control their own destinies without foreign domination. It is especially interested in the developement of educational institutions directed toward meeting the needs of the entire community. Much of this assistance to education is in the form of scholarships and fellowships, the development of libraries and the exchange of teachers and students among the various countries. It sponsors a weekly newspaper, *The Asian Student*, prepared by Asians and circulated among Asians studying in this country.

Under the sponsorship of the Asia Foundation Dr. Munawar Ali, president of the Pakistan Association of Surgeons and hon. professor of surgery at Dow Medical College, has been touring America with Mrs. Ali, who is general secretary of the All Pakistan Women's Association, Karachi Branch. Dr. Ali's purpose is partly to study American medical institutions, partly to find positions in which Pakistani medical graduates may add to their training in this country. In the currency of good will and enlightenment on the problems of Asia in the post-war world Dr. and Mrs. Ali are making a significant contribution.

## RICHARDSON OF NAUSET MARSH

THE recently published collection of essays by the late Dr. Wyman Richardson* should find a warm welcome among all who were acquainted with him personally or through the series of his writings in the *Atlantic Monthly*, as well as among the medical fraternity in general. In 1912 Dr. Richardson "began to haunt" the Nauset Marsh, on Cape Cod, and in his house there he recorded, through the years, his thoughts, serious and humorous, his philosophy and, above all, his keen-eyed observations of nature in all its forms.

These vivid pages describe, from intimate experience and with deep relish, every phase of Nauset Marsh and the creatures living there: the swift, bold flight of the gyrfalcon and the less dramatic but equally impressive ways of the plover, the night heron and the curlew, to say nothing of the "dainty ballet of the feeding petrel." One tastes the salty air and sees the flash of butterflies in the sun and hears the homely noise of the cricket or the "Who? Who?" of a horned owl; one feels again the "nor'wester . . . a fighting man's wind" and the nagging, treacherous "cussed sou'wester." On occasion the anecdotes of wild things and accounts of their habits are interrupted by a humorous application of the lesson to the doings of mankind: "Perhaps birds and animals are more intelligent than man thinks — and man less so."

This book, handsome in format and charmingly illustrated, is a worthy record of a distinguished physician and gifted essayist. His like will not soon be encountered again, but one cannot help believing that part of him still inhabits the house he loved. As he himself says of the greatest of falcons, "I am sure the memory of those rolling downs, of that exquisite, open-water Nauset Marsh, of the wide ocean, whose deep blue color defies description — I am sure the memory of all this will sometime bring him back."

*Richardson, W. *The House on Nauset Marsh*. 223 pp. New York: W. W. Norton & Co., Inc., 1955.

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Extirpation of the Uterus. — *Dr. Reiche states that he has extirpated the entire uterus seven times; and in all cases the result was fatal. He, however, advocates the operation in cases of cancer confined to the organ.*

Boston M. & S. J., *July 26, 1855*

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## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

GRIMES — Loring Grimes, M.D., of Swampscott, died on June 19. He was in his seventy-fifth year.

Dr. Grimes received his degree from Harvard Medical School in 1904. He was a member of the American Medical Association. He was past president of the South Essex District Medical Society and chief surgeon at the Lynn Hospital.

He is survived by two sons, one daughter and eight grandchildren.

HOLMES — John F. Holmes, M.D., of Manchester, New Hampshire, died on June 19. He was in his seventy-eighth year.

Dr. Holmes received his degree from Tufts University School of Medicine in 1909. He was a fellow of the American Medical Association and of the American College of Surgeons. He was a nonresident member of the Massachusetts Medical Society.

He is survived by his widow and two sons.

## CORRESPONDENCE

### A DOCTOR'S DECALOGUE

In this dynamic age of frenzied research, it is fitting for us to ponder that patients are not guinea pigs and that the practice of medicine is still a difficult art. It is often hampered by theories that, instead of enlightening the practitioner, confuse or mislead him. He is goaded to meddle with the unknown elements of human physiology while his attention is distracted from the known. Science, in the guise of the laboratory, should be recognized as an innocent handmaid, "sober, steadfast and demure," and well qualified to aid, not to guide, the clinician. When impersonated by quasi-science her role becomes that of a barmaid, "buxom, blithe and debonair." Such seductiveness is not easily resisted.

The thoughtful doctor is ever mindful of the healing power of nature, involving processes obscure and complex. He realizes that his skill would avail but little if the operative wound were merely closed with sutures by man, not sealed and healed by nature. The failure of both lay and medical men to bear in mind this reparative property of all living things accounts for such false reasoning as *post hoc, ergo propter hoc.*

Here are the ten guides to rational management with brief commentaries:

1. *Specific remedies,* those directed at the presenting cause of a particular malady, call for prompt and intensive application. This simple rule has been broken repeatedly or heeded belatedly for two general reasons: the changes in practice wrought by the growth of medical knowledge and technology; and the failure of the practitioner to determine the presenting cause, which may be primary, predisposing or underlying or the secondary, exciting or immediate or a complication of an undiagnosed condition.

2. *Nonspecific remedies,* those directed at the effects of an ailment, should be given with caution and deliberateness. The dangers involved in this rule, the converse of the first, are twofold: concealing diagnostic clues and overlooking the essential etiology. Since errors of commission are more discreditable than those of omission, one rarely should yield to the demands of impatient patients for sheer palliative treatment.

3. *The efficiency of a mode of therapy* may be ascertained only by its administration in sufficient amounts to produce either the desired or untoward effects. Though axiomatic, this principle is not infrequently disregarded because no 2 cases are actually identical.

4. *The inefficiency of a modality* indicated for a particular affection may be due to a phase or a complication not amenable to it. Patients have been allowed to suffer for several weeks before obtaining relief by the spontaneous evacuation of the products of infection. Such a contingency warrants constant alertness and vigilance as well as discretion in the selection of the most appropriate medicine.

5. *The indiscriminate use of new drugs and methods,* stemming from pure theory or inconclusive experimentation, should be avoided by all but those especially qualified for research and possessed of facilities for adequate controls. Today, practitioners are prone to relinquish the true and tried for the untrue and untried. Innovations in medicines vie with those in feminine fashions.

6. *Only one remedy of a kind being tested* for its effectiveness should be administered for a particular purpose. The superabundance of new kinds and new brands of therapy nowadays encourages resort to multiple measures. If the time element in the action of the drug initially prescribed is borne in mind therapeutic substitutes or accessories may be wisely prescribed at regular intervals. Synergism, based on empiricism, does not justify stereotyped management or relaxation in attention.

7. *The patient's emotional status* should receive proper consideration. If he suffers from a psychosomatic disorder the course indicated is determined by its reversibility or lack of it. This depends on whether the exciting cause is removable or irremovable. If the former the regimen of choice is medical; if the latter it is surgical.

8. *The patient's intelligence* must often be appraised. For, the higher it be, the more he can be trusted to do for himself, and the more liberties he can be given. In disorders that are less detectable or less understandable, he can safely be advised to heed his feelings and to be governed by his instinctive reactions. Thus, he will escape such undue restraints as those imposed on many a patient by every medical generation.

9. *Complete sociologic data* may prove adequate for the solution of certain baffling diagnostic problems before resort to burdensome, exhaustive, synthetic examination and study. They may be solved readily with the aid of the "four pedestals" on which rest health and happiness: "Work and Play, Love and Worship," so well discussed by Richard Cabot in his handy book, *What Man Lives by.*

10. *An optimistic attitude and mien* are invariably desirable for the sake of the patient and of some, if not all, of his family. At times it may be necessary for the reputation of the physician, whose mistaken prognoses are remembered longer than his correct ones.

With the aegis of this decalogue promoting personal and rational care of the patient, and with the strict observance of the solemn Oath of Hippocrates, clinicians may forestall the threatened metamorphosis of our inviolable profession into a stereotyped mercantile or governmental service.

GILBERT W. HAIGH, M.D.
Worcester, Massachusetts

### MOBILIZATION OF NOR-EPINEPHRINE

*To the Editor:* I read with considerable interest the article, "Management of Postoperative Pseudomembranous Enterocolitis with Shock: Report of a case with recovery," written by Jonassen, Fierst and Cincotti and published in the May 12 issue of the *Journal.* The patient described received nor-epinephrine for some ninety-six hours, and this drug was discontinued on the ninth postoperative day. Subsequently, on the evening of the fourteenth postoperative day, a paroxysmal episode of hypertension was noted. In their discussion of this case the authors explain this hypertensive episode as follows: "The acute episode of hypertension can be explained by a sudden marshaling of the nor-epinephrine from the extracellular pool when fluid was mobilized after diuresis."

In my limited experience with nor-epinephrine in the management of shock, I have been impressed not only by the rapidity of its onset of action but also by the rapidity with which action ceases when the drug is discontinued. In the *Medical Clinics of North America* (March, 1954) Solokoff et al., discussing the pharmacology of nor-epinephrine, make similar comment on this rapidity of onset and cessation of activity.

Although it is possible that nor-epinephrine becomes, in some manner, sequestered in "the extracellular pool," it seems remarkable to me that it should retain its pharmacologic effectiveness for some five days. That increase in urine output did occur coincidentally with the hypertensive episode is interesting, but examination of the authors' fluid-balance chart (Fig. 2) indicates that for the first two days of diuresis — that is, the fourteenth and fifteenth postoperative days — there was a negligible increase in total fluid loss over the preceding day's loss and that the increase in urine flow appeared to be at the expense of a decrease in fecal fluid loss. These facts seem to raise the question of whether, indeed, any "extracellular pool" was mobilized.

I must, in short, confess to a certain degree of puzzlement concerning this hypertensive episode and its relation to

exogenous nor-epinephrine. I should like very much to know further details of how the authors arrived at their conclusions.

KEVIN HILL, M.D.

Belgrade Lakes, Maine

## TREATMENT OF PITUITARY ADENOMAS

*To the Editor:* I recently read the article, "Present-Day Treatment of Pituitary Adenomas," which appeared in the March 31 issue of the *Journal*, and I should like to comment on the short discussion on page 526. Perhaps these comments may be of interest to readers of the *Journal*.

The tenor of the discussion is that only with a 2,000,000-volt apparatus and rotation therapy is it possible to deliver 4000 r to the tumor without large areas of permanent depilation and intense radiation reaction in the skin. It is widely known that the possession of a 2,000,000-volt apparatus, though highly desirable, is not a prerequisite to the administration of this dosage level without permanent loss of hair or intense skin reaction.

We have treated 13 such patients with tumor doses of 4000 to 6000 r at the rate of 1000 r per week with 250 KVP, half-value layer 1.7 mm. of copper, using a rotation chair. None of these patients received a moist desquamation. In all, there was regrowth of hair after temporary depilation.

It would be of interest to know if depilation occurred in the patients treated by 2,000,000 volts. Also, was the dosage rate with the 2,000,000-volt apparatus about 1000 r per week?

The advantages that a 2,000,000-volt machine of any design has over conventional deep-therapy x-ray generators is shared by all high-energy equipment such as cobalt$^{60}$, the linear accelerator and the betatron. Each has its advantages and disadvantages, which are purely physical. There is at present no evidence of any biologic advantage as far as the effect on the tumor is concerned. All these generators, however, permit the delivery of higher doses in certain areas of the body where conventional apparatus falls short. This is not true in pituitary treatment.

MORTON M. KLIGERMAN, M.D.
Radiologic Service

Presbyterian Hospital
New York City

Dr. Kligerman's letter was submitted to one of the authors of the paper in question, who offers the following reply:

*To the Editor:* Regarding the letter from Dr. Morton Kligerman, I wish to make an explanation and also answer the several questions raised.

In the first place, in stating that permanent epilation would occur from using 200 kv apparatus to deliver 4000 to 6000 r tumor dose to the pituitary gland we said "the usual 200 kv machine" and meant the usual multiportal 200 kv technic and not rotation with 200 kv apparatus.

Dr. Kligerman admits that skin reaction with temporary epilation occurs with his 200 kv rotational technic at a tumor-dosage rate of 1000 r per week. Can he be certain that epilation will always be temporary, or that there will be no late sequelae?

With 2MEV generators and rotational technics we do not get epilation after delivering 4000 to 5000 r tumor dose through fields of 4 or 5 cm. at a dosage rate of 1200 r per week. We consider the use of 2MEV x-rays and rotational technic ideal in pituitary adenomas because they represent a typical situation in which a relatively deep-seated, small lesion can be given a high dose without even temporary epilation. One should not forget that these are benign lesions with long-term survivals in which late sequelae are possible. A method that can deliver a dosage that we both agree to be necessary and that does not cause any skin reaction ought to be favorably accepted by everyone as being a superior method.

MAGNUS I. SMEDAL, M.D.

Boston

## RESTORATION OF REGISTRATION

*To the Editor:* At the meeting of the Board of Registration in Medicine held June 16, 1955, it was voted to restore the registration to practice medicine to Dr. Herman Schwartz, 11 Monmouth Court, Brookline (formerly of 500 Boylston Street, Boston).

ROBERT C. COCHRAN, M.D.
*Secretary*

State House
Boston

## BOOK REVIEW

*The Diagnosis and Treatment of Convulsive Disorders in Children.* By Samuel Livingstone, M.D., assistant professor of pediatrics, Johns Hopkins University School of Medicine, physician-in-charge, Johns Hopkins Hospital Epilepsy Clinic, and electroencephalographer, Johns Hopkins Hospital Laboratory of Electroencephalography, associate attending physician in pediatrics and assistant physician in medicine, Sinai Hospital, Baltimore, Maryland. 8°, cloth, 314 pp., with 71 illustrations. Springfield, Illinois: Charles C Thomas, 1954.

This volume is a timely addition to the treatment of epilepsy in children. The author has had a wide experience in charge of a special clinic at the Johns Hopkins Hospital and his monograph is based on a study of over 4000 children with seizures. More than half of these patients had cryptogenic epilepsy. There is further consideration given to the diagnosis of both primary and secondary epilepsy, the precipitating factors, electroencephalography and drug and dietary treatment. Additional chapters on the social management of epileptics and another on surgical treatment add to the value of this book. This volume may be considered as an outstanding contribution based on a careful study of a large number of patients. The illustrations are clear, the references full and the index adequate. It should be of great use to both the general practitioner and the pediatrician.

HENRY R. VIETS, M.D.

## BOOKS RECEIVED

**The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additonal information in regard to all listed books will be gladly furnished on request.**

*Prefrontal Leucotomy and Related Operations: Anatomical aspects of success and failure.* By Alfred Meyer, M.D. (Bonn), professor of neuropathology, Department of Neuropathology, Maudsley Hospital, University of London; and Elizabeth Beck, research assistant, Institute of Psychiatry, Department of Neuropathology, Maudsley Hospital, University of London. 8°, cloth, 60 pp., with 20 illustrations including 8 plates and 18 tables. Springfield, Illinois: Charles C Thomas, 1954. $2.25.

The authors base their paper on the William Ramsay Henderson Lecture that Dr. Meyer delivered on March 10, 1953. They discuss methods and materials, anatomy and clinicoanatomic analysis. Lists of references are appended to the parts. The tables concern predominantly affective conditions, paranoid and schizophreniform psychoses beginning before and after thirty-five years of age and under thirty-five years and miscellaneous matters. These tables are an analysis of cases. The printing was done in Great Britain.

*The Practice of Sanitation.* By Edward Scott Hopkins, principal associate engineer, Bureau of Water Supply, Baltimore, Maryland, and instructor, McCoy College, Johns Hopkins University; and Wilmer Henry Schulze, director, Sanitary Section, Baltimore City Health Department. Second edition. 8°, cloth, 466 pp., with 123 illustrations and 33 tables. Baltimore: Williams and Wilkins, 1954. $8.00.

In this new edition a book first published in 1951 and reprinted in 1953 has been brought up to date to present the pertinent facts comprising sanitation practice today in the United States. Lists of references are appended to the chapters, and there is a good index. The publishing is excellent. The book is recommended for all medical libraries.

## NONCLINICAL NOTES

### AMERICAN NEUROLOGICAL ASSOCIATION

At the eightieth annual meeting of the American Neurological Association held in Chicago, June 13-15 the following officers were elected: president, Dr. J. M. Nielsen; president-elect, Dr. H. Houston Merritt; first vice-president, Dr. James W. Kernohan; second vice-president, Dr. Robert B. Aird; secretary-treasurer, Dr. Charles Rupp; and assistant secretary, Dr. William F. Caveness.

### NEW ENGLAND ROENTGEN RAY SOCIETY

At the annual meeting of the New England Roentgen Ray Society, the following officers were elected for the year 1955-1956: president, Dr. Max Ritvo; vice-president, Dr. A. B. Soule, Jr.; treasurer, Dr. Magnus I. Smedal; and secretary, Dr. Raymond A. Dillon.

## NOTICES

### AMERICAN CANCER SOCIETY GRANTS IN CANCER RESEARCH

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is accepting application for grants-in-aid for cancer research in the United States. Applications received before October 1 will be considered during the winter, and grants recommended will become effective July 1, 1956. Further information may be obtained from the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

### AMERICAN UROLOGICAL ASSOCIATION

The American Urological Association announces the annual award of $1,000 (first prize $500, second prize $300 and third prize $200) for essays on the result of clinical or laboratory research in urology. Competition is limited to urologists not more than ten years from graduation and to men in training to become urologists. The essay awarded first prize will be presented at the meeting of the American Urological Association, Hotel Statler, Boston, Massachusetts, May 28-31, 1956. Essays must be received by the executive secretary before December 1, 1955. Further information may be obtained from the executive secretary, William P. Didusch, 1120 North Charles Street, Baltimore, Maryland.

### PHI DELTA EPSILON FRATERNITY GRADUATE CLUB PROGRAM

The program of the Graduate Club of Boston of the Phi Delta Epsilon Medical Fraternity for the coming year is as follows:

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| October 26. | Combined dinner. |
| November 30. | Cocktail party. |
| January 25. | Speaker. |
| March 21. | Initiation. |
| April 26. | Dance. |

### ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The sixty-second annual convention of the Association of Military Surgeons of the United States will be held at the Hotel Statler, Washington, D. C., November 7-9, 1955. During the honors-night dinner on November 9, the following medals and awards will be presented: the Sir Henry Wellcome Medal and Prize, the Gorgas Medal, the Stitt Award, the McLester Award, the Louis Livingston Seaman Prize and the Founder's Medal. Further information may be obtained from the Association Office, Suite 718, New Medical Building, 1726 Eye Street, N. W., Washington 6, D. C.

### AMERICAN ACADEMY OF PEDIATRICS

The annual meeting of the American Academy of Pediatrics will be held at the Palmer House, Chicago, Illinois, October 3-6. Round-table discussions will also be held October 3-6, with the seminars on October 1 and 2. Early reservations are suggested for any course, and for the banquet, which is optional. Further information may be obtained from Dr. E. H. Christopher, 610 Church Street, Evanston, Illinois.

### AMERICAN MEDICAL WRITERS' ASSOCIATION

A program sponsored by the American Medical Writers' Association will be presented in Chicago, Illinois, September 30 through October 1. Many phases of medical writing will be covered by the speakers. Further information may be obtained from Dr. Lee D. van Antwerp, president, American Writers' Association, Chicago, Illinois.

### SOCIETY MEETINGS AND CONFERENCES

July, August and September. Beth Israel Hospital Course. Page 509, issue of March 24.
July 28–August 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1099, issue of June 23.
August 28–September 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
August 30 and 31 and September 1. New England Health Institute. Page 1010, issue of June 9.
September 12–21, December 5–14, 1955, January 30–February 8, March 19–28 and June 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
September 30–October 1. American Medical Writers' Association. Notice above.
October 1 and 2 and 3-6. American Academy of Pediatrics. Notice above.
October 6-8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.
October 10-21. New York Academy of Medicine. Graduate Fortnight. Page 84, issue of July 14.
October 22-26. American Heart Association. Scientific Session. Page 603, issue of April 7.
October 23-27. American Institute of Dental Medicine. Page 414, issue of March 10.
November 1-3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.
November 6-13. Second International Congress of Allergology. Page 157, issue of January 27.
November 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.
November 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.
November 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
November 29–December 2. Interim Session of the American Medical Association, Boston.

### CALENDAR FOR THE WEEK BEGINNING THURSDAY, JULY 28

THURSDAY, JULY 28
*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00-10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00-11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Thoracic Conference. Evolution of Heart Surgery (Colored-Movie Demonstration). Dr. Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*(Concluded on page xxvii)*